NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for ALCOHOLIC BEVERAGE CONSUMPTION

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NTP Report on Carcinogens Listing for Alcoholic Beverage Consumption

Carcinogenicity

Consumption of alcoholic beverages is *known to be carcinogenic to humans* based on human studies that indicate a causal relationship between consumption of alcoholic beverages and an increased risk of cancer in humans (reviewed in IARC, 1988; Longnecker and Enger, 1996). Studies indicate that the risk is most pronounced among smokers and at the highest levels of consumption.

Consumption of alcoholic beverages is causally related to cancers of the mouth, pharynx, larynx, and esophagus. Cohort and case control studies in a variety of human populations are notable for their consistency in reporting the presence of moderate to strong associations with dose-response relationships for these four sites. Evidence also supports a weaker but possibly causal relation between alcoholic beverage consumption and increased risk of cancers of the liver and breast (Longnecker, 1994). The effect of a given level of alcoholic beverage intake on absolute risks of cancer of the mouth, pharynx, larynx, and esophagus is influenced by other factors, especially smoking. However, smoking does not explain the observed increased risk of cancers associated with increased alcoholic beverage consumption.

No adequate experimental animal carcinogenicity studies of alcoholic beverages have been reported in the literature. Studies specifically examining the carcinogenicity of ethanol in animals have not yielded results that would suggest that the ethanol component of alcoholic beverages is solely responsible for the increases in cancer observed in people consuming alcoholic beverages.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Increased frequencies of chromosomal aberrations, sister chromatid exchanges, and aneuploidies have been found in the peripheral lymphocytes of alcoholics. Ethanol-free extracts of some alcoholic beverages induced sister chromatid exchanges in human cells *in vitro* and mutations in bacteria (IARC, 1988).

The mechanism by which consumption of alcoholic beverages can cause cancers in humans is not established.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL COMPOSITION

The chemical composition of alcohol beverages was addressed by IARC (1988). Ethanol and water are the main constituents of most alcoholic beverages. The amount of ethanol consumed in a standard measure of most drinks is similar for beer, wine, and spirits (10-14 g). The ethanol in these beverages comes from the fermentation of carbohydrates by yeast. Although ethanol can be chemically synthesized from ethylene, alcohol synthesis for use in beverages is not employed by the alcoholic beverage industry because of the presence of impurities from the synthetic process.

1.1 Physical-Chemical Properties of Ethanol

Property	Information	Reference
Color	clear, colorless liquid	IARC (1988)
Boiling Point	78.5 °C	IARC (1988)
Melting Point	-114.1 °C	IARC (1988)
Density	d_4^{20} 0.789	IARC (1988)

Beer, wine, and spirits also contain volatile and nonvolatile flavor compounds that originate from raw materials, fermentation, wooden casks used for maturation, and synthetic substances added to specially flavored beverages. The exact composition of many beverages is confidential business information, though much published data defines the organic compounds usually present at low levels. Components and contaminants identified in beer, wine, and spirits were noted by IARC (1988) and several of these are known or suspected animal or human carcinogens, including acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate, asbestos, and arsenic compounds (Table 1-1).

1.2 Beer

Carbonyl compounds have been identified in beer produced in the United States, Germany and Norway; acetaldehyde was found to be the most common carbonyl compound with reported levels as high as 37.2 mg/L (Nykänen and Suomalainen, 1983; cited by IARC, 1988). Formaldehyde was also detected at lower levels.

Several nitrosamines have been identified in beer, including *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodipropylamine (NDPA), *N*-nitrosopyrrolidine, and *N*-nitrosoproline (Klein, 1981; cited by IARC, 1988).

Aflatoxins have been detected in Kenyan beer samples at concentrations of 1-2.5 μg/L; the source was believed to be rejected maize (Peers and Linsell, 1973; cited by IARC, 1988). Ochratoxin A and zearalenone were found in Kenyan beer made from contaminated barley (IARC 1983; cited by IARC, 1988).

Ethyl carbamate (urethan), a product of the reaction of ethanol and carbamyl phosphate, has been detected in commercial ales (Ough, 1984; cited by IARC, 1988).

Asbestos fibers have been identified in Canadian and U.S. beers (Cunningham and Pontefract, 1971; cited by IARC, 1988). The fibers in Canadian beer were described as chrysotile and the fiber concentrations in Canadian and U.S. beers were reported as 1.1-6.6 million fibers/L.

1.3 Wine

Acetaldehyde has been detected at 50-160 mg/L in wines produced in different countries (Nykänen and Suomalainen, 1983; Postel et al., 1972b; both cited by IARC, 1988). All aldehydes can be chemically bound to ethanol, higher alcohols, and the additive sulfur dioxide (IARC, 1988).

The nitrosamine NDMA was identified in 33 wine samples at concentrations of < 0.05-0.6 μg/L (Klein, 1981; cited by IARC, 1988). NDEA was detected in one sample at a concentration of 0.3 μg/L, but NDPA was not detected.

The fungi that produce aflatoxins may occur on grapes, since a wide variety of molds normally inhabit grapes. Consequently, wine samples were analyzed for the presence of aflatoxins (IARC, 1988). Aflatoxin B_1 was detected in two of 33 German wines at concentrations of < 1 μg/L (Schuller et al., 1967; cited by IARC, 1988). Aflatoxins were also identified in 16 of 22 wines from different countries at concentrations of < 1-2.6 μg/L (Lehtonen, 1973; cited by IARC, 1988). Using improved methods in later studies, aflatoxins were not detected in samples of French red wine, Spanish sherry, madeira and port wine (Drawert and Barton, 1974; Lemperle et al., 1975; both cited by IARC, 1988).

Since ethyl carbamate is expected to be present in most fermented beverages, some wine samples were analyzed for this compound (IARC, 1988). Ethyl carbamate was reported by Ough (1984; cited by IARC, 1988) to have been found in experimental wine (0.6-4.3 μg/L) and commercial wines (0.3-5.4 μg/L).

Asbestos fibers may be present in alcoholic beverages from filters used for clarification, water used during production processes, and from asbestos-cement water pipes (IARC, 1988). Asbestos fibers have been identified in European and Canadian wine, but concentrations were not reported (Cunningham and Pontefract, 1971; cited by IARC, 1988).

Arsenic was analyzed in wine samples because of the use of arsenic-containing fungicides (IARC, 1988). Arsenic was reported in nine U.S. wines at concentrations from 0.02-0.11 mg/L (Noble et al., 1976; cited by IARC, 1988). Arsenic concentrations in Spanish wine were shown to decrease after processing (Aguilar et al., 1987; cited by IARC, 1988), and the arsenic content of German wines has been ~0.009 mg/L since 1970 (Eschnauer, 1982; cited by IARC, 1988).

1.4 Spirits

Acetaldehyde occurs in all spirits because it is easily distilled with water; greater than 90% of the total aldehyde content is acetaldehyde (IARC, 1988). Concentrations reported in several whiskeys ranged from 20-220 mg/L, and the concentration in brandy has been found to be as high as 600 mg/L (Nykänen and Suomalainen, 1983; cited by IARC, 1988).

Many investigations have determined nitrosamine occurrence in alcoholic beverages (IARC, 1988). The nitrosamines NDMA, NDEA, and NDPA were detected in white alcohol, whiskey, rum, and cognac, with concentrations ranging from < 0.05 μg/L-4.8 μg/L (Klein, 1981; cited by IARC, 1988).

Because of the high concentration of urethan detected in some fruit brandies (0.1-7.0 mg/L), this substance was analyzed in other distilled spirits (IARC, 1988). Whisky, rum, cognac, sherry, and liqueur were reported to contain ethyl carbamate at concentrations ranging from 0.02-0.16 mg/L (Mildau et al., 1987; cited by IARC, 1988).

Table 1-1. Potential Carcinogens Identified in Alcoholic Beverages

Beverage	Components	Reference
Beer	acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate, asbestos fibers	IARC (1988)
Wine	acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate, asbestos fibers, arsenic compounds	IARC (1988)
Spirits	acetaldehyde, nitrosamines, ethyl carbamate	IARC (1988)

2.0 HUMAN EXPOSURE

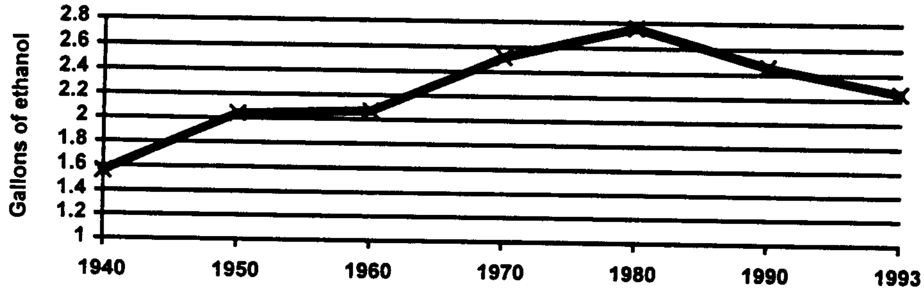
2.1 Use

IARC (1988) describes in detail the use of alcoholic beverages (Appendix B). Consumption trends, including overall level of alcohol consumption, beverage choice, age and sex differences, and temporal variations, differ among and within societies. Patterns of alcohol consumption have been observed to vary on a global scale, largely independent of regional differences or economic and social changes (IARC, 1988).

A downward trend in alcohol consumption was observed in the United States and many European countries from the turn of the twentieth century until the period between the world wars. Alcohol consumption then increased, approaching the peak levels of the nineteenth century, until the 1970s and 1980s when consumption rates slowed, leveled off or, in some countries (including the United States, Canada, Germany, Italy, Spain, France, Australia, and New Zealand), decreased. Overall increases in consumption were observed in some other countries (Denmark, Finland, Great Britain, Japan, and Luxembourg) over the same period. The authors note that alcohol consumption in these countries was initially (in 1970) very low in comparison to the other countries studied (NIAAA, 1997).

Alcohol consumption in the United States increased from the 1940s until the early 1980s, then began to steadily decrease; by 1993, consumption had declined to the lowest level since 1964 (Table 2-1). Per capita consumption figures for Table 2-1 were derived by estimating total alcohol use, based on sales and shipment data, of the U.S. population aged 14-years or older. Apparent per capita consumption is expressed in gallons of pure alcohol (NIAAA, 1997).

Table 2-1. Total per capita alcohol consumption United States, 1940-1993



Source: Williams et al. (1995); cited by NIAA (1997)

A 1990 National Alcohol Survey gathered data regarding the demographic distribution of drinking patterns in the United States (Midanik and Clark, 1994). Respondents were classified as current drinkers (any use of alcohol beverages in the preceding year), weekly drinkers (any alcoholic beverage use at least weekly during the preceding year), and drinkers of five or more drinks (drinking five or more drinks on one occasion weekly or more often during the preceding year).

Of the men surveyed, 71.2% were current drinkers, 40.0% were weekly drinkers, and 6.5% were in the five drinks group. In the group reporting the highest alcohol consumption, men aged 18-29, 76.5% were current drinkers, 44.4% were weekly drinkers, and 11.0% were in the five drinks group. The same age group reported the highest consumption among women: 69.7% were current drinkers, 19.7% were weekly drinkers, and 3.0% were in the five drinks group. When data from all age groups of women were combined, 59.4% were current drinkers, 18.8% were weekly drinkers, and 1.4% were in the five drinks group. These figures all represent decreases in alcohol consumption as measured by a similar survey conducted in 1984 (Midanik and Clark, 1994).

Respondents were grouped by ethnicity and religious affiliation (Table 2-2). The survey found no statistically significant differences in alcohol use among ethnic groups, but conservative Protestants reported significantly lower alcohol consumption in all three categories.

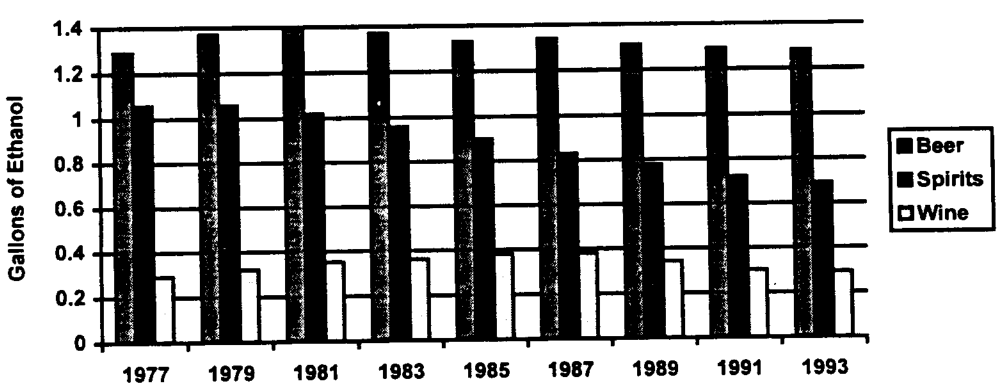
Table 2-2. Demographic Characteristics of U.S. Drinkers 1990: Ethnicity and Religion—Percentage of Drinkers in Groups

	Current Drinkers	Weekly Drinkers	Drinkers of Five or More Drinks
Race			
Black	61.6	25.8	3.5
White	65.9	30.2	3.5
Hispanic	66.6	26.5	8.9
Other	57.0	21.6	1.4
Religion			
Catholic	78.6	37.3	6.7
Jewish	91.8	30.2	0.0
Liberal Protestant (excessive alcohol use discouraged)	72.6	36.1	1.0
Conserv. Protestant (all alcohol use discouraged)	51.1	19.3	2.2
Other	75.4	37.1	9.3

Source: Midanik and Clark (1994)

Per capita consumption of wine and beer in the United States was relatively stable over the period beginning in the early 1980s and continuing into the 1990s when overall alcohol consumption was falling (Williams et al., 1995; cited by NIAAA, 1997). Most of the decrease in U.S. alcohol consumption can be attributed to decreased consumption of spirits. Though wine has made much less of a contribution to the total volume of U.S. alcohol consumption than beer or spirits, per capita consumption of wine was the same in 1993 as it was in 1977, while consumption of spirits fell by almost 35% over the same period. Per capita consumption of beer decreased from 1981 to 1985, fluctuated thereafter, and in 1993 was one percent below 1977 consumption levels (NIAAA, 1997) (Table 2-3).

Table 2-3. Per capita alcohol consumption by beverage type United States, 1977-1993



Source: Williams et al. (1995); cited by NIAAA (1997)

Per capita consumption of absolute alcohol is highest in Europe. Based on data for 1982-1991, France had the highest average per capita consumption at 13.1 liters (3.4 gallons) (ARF, 1994). In other parts of the world, especially in countries where Islam is the major religion, per capita consumption of alcohol is well below this level, although increases have been noted in some countries in recent years.

2.2 Production

IARC (1988) summarized data on worldwide production of alcoholic beverages including kinds of beverage, and production methods (Walsh and Grant, 1985; cited by IARC, 1988). All alcoholic beverages are produced by the fermentation of fruit or other vegetable matter. Most commercial and home production involves fermented beverages that are classified, based on raw materials and production methods used, as beer, wine, or spirits, although smaller quantities of other kinds of fermented beverages (cider, rice wine, palm wine, etc.) are also produced. Beer is produced by fermentation of malted barley or other cereals with the addition of hops. Wine is made from fermentation of grape juice or crushed grapes; fortified wines include additional distilled spirits. Distilled spirits, so named because of liquid distillation after sugar fermentation to increase the alcohol content, originate from sources of starch or sugar, including cereals, molasses from sugar beets, grapes, potatoes, cherries, plums, and other fruits.

Estimates of alcoholic beverage production in each region of the world in 1990 are listed in Table 2-4. Totals in this table may not match due to rounding of original data.

Table 2-4. World Alcoholic Beverage Production, 1990

	Africa	America	Asia	Europe	Oceania	World Total
Wine (in thousand metric tons)	1070	4520	254	22673	494	29010
Beer (in thousand hectoliters)	57265	374529	165955	466739	24254	1088742
Spirits (in thousand hectoliters)	1203	18454	14284	22992	823	57756

Source: ARF (1994)

2.3 Regulations

A March 1999 search of the most recent editions of the *Code of Federal Regulations* found no regulations requiring warnings on alcoholic beverage labels of an increased risk of cancer due to alcoholic beverage consumption. (Labels on saccharin-containing wines, distilled spirits, and malt beverages, however, must warn of a cancer risk from saccharin consumption [27 CFR 4.32, 5.32, and 7.22, respectively, enforced by the Bureau of Alcohol, Tobacco and Firearms, Department of the Treasury]).

FDA regulates health claims information on food labels. Thus, labels on low fat foods may make the health claim that diets low in fat "may" or "might" reduce the risk of some cancers with several provisions (21 CFR 100.73 Health claims: dietary lipids and cancer). Optional information allowed includes identification of risk factors for development of cancer. Alcohol consumption is one of the risk factors that FDA lists. The same optional information may be added to labels stating there is a reduced risk of cancer for diets high in fiber-containing grain products, fruits, and vegetables (21 CFR 101.76, 21 CFR 101.78).

3.0 HUMAN STUDIES

Recent investigations, including a review of new epidemiological data (Longnecker and Enger, 1996), reinforce previous reports of a causal relationship between alcoholic beverage consumption and cancers of the oral cavity, pharynx, larynx, esophagus, and liver (IARC, 1988). Estimated relative risks were significantly higher for cancers of the mouth, pharynx, larynx, esophagus, breast, and liver among consumers of alcoholic beverages, particularly among heavy drinkers. An association between increased risk of breast cancer and alcohol intake has been established, but conclusions regarding causality cannot be drawn in the absence of an established mechanism (Longnecker and Tseng, 1999). The effect of all defined levels of alcohol intake on absolute risks cancers of the mouth, pharynx, larynx, and esophagus was influenced by other risk factors, especially smoking. Large bowel cancers had a weak association with alcoholic beverage consumption, while melanoma and cancers of the bladder, stomach, ovary, and endometrium were not consistently related to alcohol intake (Longnecker and Enger, 1996; Westerdahl et al., 1996).

Results of 59 of the largest (defined by number of cases) case-control and cohort studies of the relationship between alcohol consumption and risk of oral and pharyngeal, esophageal, laryngeal, breast, and liver cancers are summarized below. Study details are presented in Table 3-1.

3.1 Oral and Pharyngeal Cancer

Nine case-control studies, each with more than 100 cases, support a strong association of alcohol drinking and oropharyngeal cancer (Elwood et al., 1984; cited by IARC, 1988; Martinez, 1969; Bross and Coombs, 1976; Brugere et al., 1986; Notani, 1988; Tuyns et al., 1988; Barra et al., 1990; Franceschi et al., 1990; Day et al., 1994), consistent with conclusions in a recent review (Longnecker and Enger, 1996). All risk estimates were adjusted for smoking which is a known risk factor for oropharyngeal cancer. The cohort studies reviewed are not included in this report because the risk estimates were not adjusted for smoking or because studies combined analysis of oropharyngeal cancer with cancer of the larynx and esophagus. However, in five retrospective cohort studies of alcoholics, the relative risk of oral and pharyngeal cancer was significantly increased (IARC, 1988).

3.2 Esophageal Cancer

Nine case-control studies with cases in excess of 100 show a strong dose-response relationship between alcohol intake and esophageal cancer (Tuyns et al., 1977; cited by IARC, 1988; Tuyns et al., 1979; Vassallo et al., 1985; De Stefani et al., 1990; Cheng et al., 1992; Franceschi et al., 1994; Gao et al., 1994; Hanaoka et al., 1994; Brown et al., 1997). As with studies of oropharyngeal cancer, risk estimates were adjusted for smoking and other potential confounders. The cohort studies reviewed are not presented because the risk estimates were not adjusted for smoking. However, seven of eight retrospective cohort studies indicate a two- to four-fold increase in esophageal cancer risk (IARC, 1988).

3.3 Breast Cancer

Six of nine case-control studies with greater than 1000 cases indicate a modest, but significant, dose-response relationship between alcohol consumption and breast cancer (Williams and Horm, 1977; Rosenberg et al., 1982; Lê et al., 1984; Harvey et al., 1987; La Vecchia et al., 1989.; Longnecker et al., 1995). All five of the cohort studies of more than 100 cases (Hiatt and Bawol, 1984; Hiatt et al., 1987; Schatzkin et al., 1987; Garfinkel et al., 1988, Smith-Warner, 1997) showed a positive association between breast cancer and alcohol consumption. Most of these studies controlled for factors known to contribute to the risk of breast cancer (e.g., reproductive factors and family history of breast cancer). The association of breast cancer and alcohol consumption is also supported by a recent meta-analysis of 38 studies (Longnecker, 1994).

3.4 Laryngeal Cancer

Ten case-control studies with more than 90 cases each support an association between alcohol drinking and laryngeal cancer (Wynder et al., 1956, 1976; Burch et al., 1981; Elwood et al., 1984; all cited by IARC, 1988; Olsen et al., 1985; Brugere et al., 1986; Tuyns et al., 1988; Choi and Kayho, 1991; Franceschi et al., 1994; Dosemeci et al., 1997). All risk estimates from these case control studies were adjusted for smoking, a known risk factor for laryngeal cancer. The cohort studies reviewed are not included in this report because information on smoking habits was not obtained. However, the risk of laryngeal cancer was significantly increased in four of six retrospective cohort studies (IARC, 1988).

3.5 Liver Cancer

Seven of ten case-control studies with 60 or more cases (Bulatao-Jayme et al., 1982; Stemhagen et al., 1983; Hardell et al., 1984; Austin et al., 1986; Yu et al., 1988; Tsukuma et al., 1990) and four cohort studies with greater than 20 cases (Jensen et al., 1980; cited by IARC, 1988; Hakulinen et al., 1974; Kono et al., 1986; Shibata et al., 1986) showed an association between liver cancer and heavy drinking. Most of these studies indicate a dose-response gradient.

3.6 Type of Alcoholic Beverage as Risk Factor

Although a number of studies compare the cancer risk associated with specific types of alcohol, the data do not support general conclusions regarding beverage specific differences.

3.7 Dose-Response Relationships

The studies summarized in Table 3-1 generally show a dose-response between alcohol beverage intake and cancer incidence at certain sites. This relationship is also apparent from qualitative analyses of published results (Longnecker and Tseng, 1999). Variations in dose-response occur among and within different countries, possibly due to differences in beverage preferences, drinking patterns, reporting of alcoholic beverage consumption, and study design.

3.8 Beneficial Effects of Low to Moderate Alcohol Consumption

Potential health benefits of low alcoholic beverage consumption should be recognized as well as the detrimental effects of heavy consumption. Light-to-moderate intake of alcoholic beverages (defined by the authors as up to 2 drinks/day) has been repeatedly associated with a reduced risk of coronary artery disease (Klatsky, 1994). Thun et al. (1997) found an association between moderate alcohol consumption (defined by the authors as ~1 drink/day) and a slightly reduced overall mortality rate in a recent study of middle-aged and elderly U.S. adults.

Table 3-1. Human Studies of Alcohol

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Oral and Pharyngeal Cancer Case-Control Studies						
population-based case-control	**Cases:** 921 males and females (black and white) with primary oral cancer **Controls:** 900 persons identified by random digit dialing or rosters provided by the Health Care Financing Administration cases and controls from four areas in U.S. less than half of controls reported ≥1drinks of wine or beer or >4 drinks of liquor per week	**Evaluation**: personal interviews with participants or next of kin (24% of cases, 2% of controls)	**Estimation**: calculation of OR for oropharyngeal cancer <u>OR (95% CI)</u> 13.2 (5.2-33.5) for heavy drinkers of light colored liquors 4.6 (2.7-7.9) for heavy drinkers of dark colored liquors 'heavy' defined by authors as 30+ drinks/wk	Adjustment was made for multiple potentially confounding factors, including smoking and other types of alcohol.	This analysis used data from a U.S. case-control study of oral-pharyngeal cancer. The original study was large and population-based.	Day et al. (1994)
case-control	**Cases:** 281 with cancer of the hypopharynx **Controls:** 3057 from general population in six areas considered (selected from census lists, electoral lists, population registries) cases and controls from Italy, Spain, Switzerland, France; average adult lifetime daily alcohol consumption was computed for cases and controls	**Evaluation:** interviews	**Estimation:** Calculated OR of hypopharynx cancer using logistic regression <u>OR (95% CI)</u> 1.57 (0.72-3.42) for 21-40 g alcohol/day 3.15 (1.58-6.24) for 41-80 g alcohol/day 5.59 (2.79-11.21) for 81-120 g alcohol/day 12.54 (6.29-25.00) for 121+ g alcohol/day	OR adjusted for smoking, age, location	alcohol effect in lowest smoke category	Tuyns et al. (1988)
case-control	**Cases:** 145 white females with cancer of the mouth and tongue **Controls:** 1973 white females with non-neoplastic diseases	**Evaluation:** interviews	**Estimation:** calculation of RR for mouth and tongue cancer <u>RR (95% CI)</u> 1.3 (0.8-2.2) for < 30 drinks/mo. 3.4 (1.7-6.6) for ≥ 30 drinks/mo.	RRs presented were adjusted for age and smoking by IARC (1988)		Bross and Coombs (1976)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 278 males with oral cavity cancers **Controls:** 392 males from hospital and general population	**Evaluation:** interviews	**Estimation:** calculated RR (95% CI) for cancer according to alcohol consumption RR for cancer of oral cavity 1.2 (0.7-1.9) for 1.9+ g/day RR for cancer of the pharynx 1.4 (0.9-2.4) for 1.9+ g/day *results for <1.9 g/day not given	adjusted for age and smoking	no dose-response evaluation	Notani (1988)
case-control	**Cases:** 305 males with cancer of oral cavity and pharynx **Controls:** 1621 males in the hospital for acute nonneoplastic conditions unrelated to alcohol consumption	**Evaluation**: reported consumption of alcoholic beverages	**Estimation**: calculation of OR for oral and pharyngeal cancer OR (95% CI) Wine, beer, and spirits 0.8 (0.3-2.3) for ≤ 55 drinks/wk) 1.8 (0.8-4.4) for 56-83 drinks/wk 4.1 (2.0-8.2) for ≥ 84 drinks/wk	OR adjusted for cigarette smoking, age, residence, occupation	Heavy alcohol consumption even in lowest exposure groups	Barra et al. (1990)
case-control	**Cases:** 108 males with oral cancer **Controls:** 108 males from same hospital or neighborhood as cases	**Evaluation:** interviews	**Estimation:** calculated RR for cancers of the lip, floor of mouth, tongue, other parts of the mouth RR (95% CI) 0.5 (0.2-1.5) for ≤ 1 unit/day 1.7 (0.7-3.9) for 2-4 units/day 2.8 (1.1-7.0) for ≥ 5 units/day unit = 2 oz. Liquor 18 oz. Beer 8 oz. Wine	Pairs matched for age and smoking	ORs shown were calculated by IARC (1988)	Martinez (1969)
case-control	**Cases:** 634 males with oropharynx cancer **Controls:** unknown number from national survey (~4000 males)	**Evaluation:** hospital chart records of alcohol and tobacco consumption compared to consumption by general population	**Estimation:** calculated RR for oropharynx cancer RR (95% CI) 1.0 for 0-39 g ethanol/day 2.6 (1.6-4.2) for 40-99 g ethanol/day 15.2 (9.2-25.1) for 100-159 g ethanol/day 70.3 (41.2-120) for 160+ g ethanol/day	RR adjusted for smoking Controls may have underreported their alcohol consumption, leading to an overestimation of the RR for alcohol.	IARC (1988) noted that information on tobacco and alcohol use was obtained by different methods and situations	Brugere et al. (1986)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 366 males with hypopharynx cancer **Controls:** unknown number from national survey (~4000 males)	**Evaluation:** hospital chart records of alcohol and tobacco consumption compared to consumption by general population	**Estimation:** calculated RR for hypopharynx cancer RR (95% CI) 1.0 for 0-39 g ethanol/day 3.3 (1.4-7.9) for 40-99 g ethanol/day 28.6 (12.5-65.1) for 100-159 g ethanol/day 143.1 (61.9-330.5) for 160+ g ethanol/day	RR adjusted for smoking The authors note that the controls may have underreported their alcohol consumption, leading to an overestimation of the RR for alcohol.	IARC (1988) noted that information on tobacco and alcohol use was obtained by different methods and in different interview situations for cases and controls.	Brugere et al. (1986)
case-control	**Cases:** 133 males and females with cancer of the tongue, gum, floor of mouth, and other cancers of the oral cavity **Controls:** 133 hospital controls other cancers presumed by the authors to be unrelated to tobacco or alcohol use	**Evaluation:** interviews	**Estimation:** calculated RR of oral cancers based on alcohol consumption per week RR (95% CI not calculated) 1.0 for < 24 g 1.1 for 24-96 g 1.4 for 120-216 g 1.8 for 240-480 g 4.5 for > 480 g	RR adjusted for smoking		Elwood et al. (1984; cited by IARC, 1988)
case-control	**Cases:** 157 males with histologically confirmed oral cancer **Controls:** 1272 males in same hospitals as cases and without alcohol-related disease	**Evaluation:** personal interviews by trained interviewers	**Estimation:** calculation of OR for oral cancer using logistic regression OR (95% CI) 1 for ≤ 19 drinks/wk 1.1 (0.5-2.5) for 20-34 drinks/wk 3.2 (1.6-6.2) for 35-59 drinks/wk 3.4 (1.7-7.1) for 60+ drinks/wk significant positive trend	OR adjusted for age, area of residence, years of education, occupation, and smoking		Franceschi et al. (1990)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Esophageal Cancer Case-Control Studies						
population-based case-control	**Cases:** 373 males (124 white, 249 black) diagnosed with squamous-cell esophageal cancer; aged 30-79 **Controls:** 1364 males (750 white, 614 black) from three geographic areas in the U.S. Response Rate = 68% cases 76% controls	**Evaluation:** interviews	**Estimation:** calculated esophageal cancer OR for black men OR (95% CI) black men 1.0 for never drank 1.7 (0.8-3.6) for < 8 liquor drinks/wk 3.8 (1.9-7.7) for 8-14.9 liquor drinks/wk 8.2 (4.2-16.3) for 15-28.9 liquor drinks/wk 10.0 (5.0-19.9) for 29+ liquor drinks/wk $p < 0.001$ also significant ($p < 0.001$) increase in OR with increasing intake of wine among black men and beer and liquor among white men	OR adjusted for age, area, smoking, income, and each type of alcoholic beverage is adjusted for amount of the other two. Other analyses adjusted for total alcohol.		Brown et al. (1997)
case-control	**Cases:** 196 males with esophageal cancer **Controls:** 1064 males in hospital without cancer	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer risk RR (95% CI) 1.0 for never consuming alcohol 1.0 (0.6-1.8) for ever consuming alcohol	RR adjusted for smoking, calculated by IARC (1988)		Bradshaw and Schonland (1974)
case-control	**Cases:** 200 males with esophageal cancer; all cases in the population between 1972-1974 **Controls:** 778 males selected randomly from same population	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer RR (95% CI could not be calculated) 1.0 for 0-20 g ethanol/day 1.2 for 21-40 g ethanol/day 3.4 for 41-60 g ethanol/day 6.1 for 61-80 g ethanol/day 6.6 for 81-100 g ethanol/day 18.3 for > 101 g ethanol/day	RR adjusted for smoking, but adjustment did not affect crude RR		Tuyns et al. (1977)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 312 males with esophageal cancer **Controls:** 869 hospital-based male controls matched by age	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer RR (95% CI not given) 1.0 for 0-20 g ethanol/day 1.11 for 21-40 g ethanol/day 2.54 for 41-60 g ethanol/day 3.59 for 61-80 g ethanol/day 9.83 for 81-100 g ethanol/day 10.90 for 101-120 g ethanol/day 11.28 for 121-140 g ethanol/day 23.36 for 141+ g ethanol/day	RR adjusted for smoking		Tuyns et al. (1979)
case-control	**Cases:** 199 males in Uruguay with esophageal cancer **Controls:** 398 hospital-matched without alcohol or tobacco-related diseases and resident of Uruguay for at least 5 yr	**Evaluation:** interviews	**Estimation:** calculated RR for esophageal cancer RR (95% CI; no. cases/no. controls) 1 (26/100) for 0 mL alcohol/day 0.85 (0.4-1.8; 16/61) for 1-24 mL alcohol/day 0.71 (0.3-1.6; 12/51) for 25-49 mL alcohol/day 1.37 (0.8-2.4; 50/117) for 50-149 mL alcohol/day 3.57 (1.9-6.7; 46/38) for 150-249 mL alcohol/day 5.27 (2.7-10.2; 49/31) for 250+ mL alcohol/day trend test significant $\chi^2 = 4.9$, 1 d.f.	RR adjusted for cigarette smoking, age, residence		De Stefani et al. (1990)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
hospital-based case-control	**Cases:** 400 males and females with esophageal cancer **Controls:** 1598 (800 from hospital and 798 from general clinics) without alcohol or tobacco-related diseases	**Evaluation:** interviews	**Estimation:** calculated OR for esophageal cancer using conditional logistic regression OR (95% CI) 1.00 for never drinker 1.07 (0.66-1.75) for < 50 g alcohol/wk 1.36 (0.67-2.74) for 50-99 g alcohol/wk 1.82 (0.99-3.35) for 100-199 g alcohol/wk 3.40 (1.92-6.01) for 200-399 g alcohol/wk 5.05 (2.72-9.39) for 400-599 g alcohol/wk 11.11 (5.40-22.85) for 600-799 g alcohol/wk 18.07 (7.40-44.13) for 800-999 g alcohol/wk 9.93 (5.27-18.74) for > 1000 g alcohol/wk	adjusted for tobacco smoking and several other factors including dietary factors		Cheng et al. (1992)
population-based case-control	**Cases:** males (624) and females (278) in Shanghai, China with esophageal cancer **Controls:** 1552 randomly selected from urban Shanghai population and matched to cases by age and sex	**Evaluation:** interviews	**Estimation:** calculated OR for esophageal cancer using unconditional logistic regression OR (95% CI; no. cases/controls) in men 1.2 (0.8-1.8; 61/103) for 1-249 g ethanol/wk 0.9 (0.6-1.3; 95/147) for 250-749 g ethanol/wk 4.0 (2.6-6.3; 134/44) for 750+ g ethanol/wk	adjusted for several factors including smoking		Gao et al. (1994)
hospital-based case-control	**Cases:** 337 males with esophageal cancer **Controls:** 1706 male inpatients with acute conditions unrelated to alcohol and tobacco consumption	**Evaluation:** interviews	**Estimation:** calculated OR using unconditional logistic regression OR (95% CI) 1 for 0 drinks/wk (reference category) 0.6 (0.27-1.29) for 1-13 drinks/wk 0.45 (0.25-0.81) for 14-27 drinks/wk 1.03 (0.60-1.76) for 28-41 drinks/wk 2.25 (1.29-3.93) for 42-55 drinks/wk 3.69 (2.19-6.22) for ≥ 56 drinks/wk	adjusted for smoking		Franceschi et al. (1994)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
hospital-based case-control	**Cases:** 185 males with esophageal cancer **Controls:** 386 males with other neoplastic conditions	**Evaluation:** interviews	**Estimation:** calculated RR of esophageal cancer RR (95% CI) 1.0 for 0-49 mL ethanol/day 4.1 (2.0-8.1) for 50-99 mL ethanol/day 7.1 (3.8-13.2) for $\geq$ 100 mL ethanol/day significant positive trend	adjusted for smoking		Vassallo et al. (1985)
multicenter hospital-based case-control	**Cases:** 141 patients with confirmed esophageal cancer **Controls:** 141; one control per case among patients in same hospital all cases and controls patients in surgical departments of seven hospitals	**Evaluation:** interviews	**Estimation:** calculated esophageal cancer risk using conditional logistic regression analyses OR (95% CI) 1.00 for $\leq$ 53 g alcohol/wk 2.19 (0.92-5.18) for > 53 g alcohol/wk 5.17 (2.13-12.55) for > 242 g alcohol/wk 5.86 (2.43-14.17) for > 414 g alcohol/wk significant ($p < 0.0001$) positive trend	OR adjusted for tobacco consumption		Hanaoka et al. (1994)
Breast Cancer Case-Control Studies						
population-based case-control	**Cases:** 6662 breast cancer patients, average age 58.7 yr, reported to one of four statewide cancer registries in the northeastern United States; response rate = 80% **Controls:** 9163 selected from state driver's license lists and Health Care Financing Administration lists of Medicare beneficiaries; response rate = 84%	**Evaluation:** telephone interviews; reliability of questionnaire assessed by reinterview after 6-12 mo. (similar responses; Spearman correlation coefficients at least 0.75)	**Estimation:** calculated RRs for breast cancer and adjusted for various factors using unconditional logistic regression RR (95% CI) 1 for 0 g ethanol/day 1.08 (0.98-1.19) for 0-5 g ethanol/day 1.09 (0.96-1.23) for 6-11 g ethanol/day 1.17 (1.01-1.37) for 12-18 g ethanol/day 1.49 (1.24-1.79) for 19-32 g ethanol/day 1.95 (1.42-2.66) for 33-45 g ethanol/day 1.96 (1.43-2.67) for > 46 g ethanol/day p for trend <0.0001	RR adjusted for age, state, age at first full-term pregnancy, parity, body mass index, age at menarche, education, benign breast disease, and family history of breast cancer		Longnecker et al. (1995)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 1010 females with breast cancer who attended private surgical clinics in France **Controls:** 1950 females selected from same clinics	**Evaluation:** interviews	**Estimation:** calculated RR RR (CI not provided; no. cases/no. controls) 1.0 (473/1105) for no alcohol with meals 1.47 (537/845; p = 0.0001) for total alcohol with meals 1.50 (20/36) for cider with meals 2.44 (14/16; p = 0.05) for beer with meals 1.44 (495/778; p = 0.001) for wine with meals	controlled for reproductive factors and dairy products		Lê et al. (1984)
case-control	**Cases:** 2402 females with histologically confirmed breast cancer Response = > 97% **Controls:** 2220 females with acute conditions unrelated to risk factors for breast cancer Response = > 97%	**Evaluation:** interviews	**Estimation:** calculated adjusted RR for breast cancer using logistic regression RR (95% CI) 1.3 (1.1-1.6) for < 1 drink/day 1.3 (1.1-1.5) for 1 to < 2 drinks/day 1.4 (1.2-1.7) for 2-3 drinks/day 2.2 (1.7-2.7) for > 3 drinks/day positive trend (p < 0.001)	RR adjusted for age, geographic area, socio-demographic variables, smoking, family history of breast cancer, nutrition and diet indicators, menstrual, reproductive, and hormonal risk factors		La Vecchia et al. (1989)
case-control	**Cases:** 1152 females with breast cancer **Controls:** 2702 females with nonmalignant disorders used data from a large drug-surveillance program in Canada, Israel, and the United States	**Evaluation:** interviews	**Estimation**: calculated RR for breast cancer with Mantel-Haenszel and multiple logistic regression RR (95% CI) 1.9 (1.5-2.4) for alcohol consumed < 4 days/wk 2.5 (1.9-3.4) for alcohol consumed ≥ 4 days/wk	RR adjusted for age and geographic area		Rosenberg et al. (1982)
case-control	**Cases:** 1314 females with breast cancer in a New York hospital **Controls**: 770 patients with nonneoplastic conditions	**Evaluation**: interviews	**Estimation:** calculated RR of breast cancer RR (95% CI not reported) 1.0 for 0 drinks/mo. (never) 0.6 for 0 drinks/mo. (ex) 1.1 for < 3 drinks/mo. 1.0 for 3-8 drinks/mo. 1.1 for 9-25 drinks/mo. 1.1 for ≥ 26 drinks/mo.	RR adjusted for age		Byers and Funch (1982)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases**: 1226 females with breast cancer identified through eight U.S. cancer registries Response Rate = 82% **Controls**: 1279 females identified through random digit phone dialing Response Rate = 85%. IARC (1988) noted that the number of controls not contacted is never known.	**Evaluation**: interviews	**Estimation:** calculated RR for breast cancer <u>RR (95% CI)</u> 1.0 for 0 g ethanol/wk (referent) 0.9 (0.7-1.2) for < 50 g ethanol/wk 0.9 (0.7-1.2) for 50-149 g ethanol/wk 1.1 (0.7-1.7) for 150-199 g ethanol/wk 1.1 (0.7-1.9) for 200-249 g ethanol/wk 1.0 (0.5-1.7) for 250-299 g ethanol/wk 1.1 (0.6-1.8) for ≥ 300 g ethanol/wk	RR adjusted for family history, reproductive factors, age, smoking, body mass index	IARC (1988) noted that alcohol questions were not clearly related to period before diagnosis. Both cases and controls reported intakes that were higher than in national surveys (reported by study authors).	Webster et al. (1983)
nested case-control	**Cases**: 1524 females with breast cancer who participated in a U.S. cancer screening program; diagnosis was at least 3 yr after entry into screening program **Controls**: 1896 females in cancer screening program who did not develop cancer	**Evaluation**: interviews	**Estimation**: calculated RR for breast cancer <u>unadjusted RR (95% CI)</u> 1.0 for no (never) ethanol consumption 1.1 (0.9-1.3) for 0.1-13 g ethanol/wk 1.1 (0.9-1.3) for 14-91 g ethanol/wk 1.3 (1.0-1.7) for 92-182 g ethanol/wk 1.7 (1.2-2.4) for > 183 g ethanol/wk	RR adjusted for education, income, and reproductive factors; adjusted estimates not different from unadjusted estimates	IARC (1988) noted that effects were associated with alcohol use before age 30	Harvey et al. (1987)
case-control	**Cases**: 1118 breast cancer patients interviewed as part of the Third National Cancer Survey in the U.S. **Controls**: 3178 males and females with cancers not associated with alcohol or tobacco consumption	**Evaluation**: interviews	**Estimation**: calculated RR for breast cancer <u>RR (95% CI not provided)</u> 1.3 ($p < 0.05$) for consumption of < 1200 g ethanol/yr 1.6 ($p < 0.01$) for consumption of > 1200 g ethanol/yr	controlled for smoking, age, and race		William and Horm (1977)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
population-based case-control	**Cases:** 3498 U.S. females with newly diagnosed breast cancer **Controls:** 3157 females randomly chosen from same geographic areas Data from the Centers for Disease Control Cancer and Steroid Hormone Study	**Evaluation:** personal interviews by trained interviewers	**Estimation:** calculated adjusted RR using logistic regression RR (95% CI) 1.0 (0.8-1.1) for < 1 drink/wk 1.0 (0.8-1.2) for 1-3 drinks/wk 0.9 (0.7-1.1) for 4-7 drinks/wk 1.1 (0.9-1.3) for 8-14 drinks/wk 1.0 (0.8-1.4) for 15-21 drinks/wk 1.2 (0.9-1.6) for 22+ drinks/wk p for trend = 0.52	RR adjusted for age, age at first full-term pregnancy, parity, age at menarche, menopausal status, benign breast disease, family history of breast cancer, menopausal status, and pack-years of smoking		Chu et al. (1989)
Breast Cancer Cohort Studies						
prospective cohort	581,321 females enrolled in a U.S. prospective study in 1959 and followed for 12 yr (92%)	**Evaluation:** study participants completed a questionnaire	**Estimation:** calculated adjusted RR for breast cancer and alcohol consumption RR (95% CI) 1.00 for no alcohol consumption 0.96 (0.82-1.13) for occasional alcohol consumption 1.18 (1.03-1.36) for 1 whiskey equivalent/day 1.06 (0.86-1.30) for 2/day 1.28 (0.95-1.74) for 3/day 1.36 (0.90-2.07) for 4/day 2.10 (1.18-3.72) for 5/day 1.60 (1.00-2.56) for 6+/day	RR adjusted for age, education, age at first pregnancy, family history of breast cancer, meat consumption, and cigarette smoking		Garfinkel et al. (1988)
prospective cohorts combined	4335 invasive breast cancer cases from seven prospective studies in Canada, the Netherlands, Sweden, and the United States	**Evaluation:** food frequency questionnaires	**Estimation:** calculated pooled multivariate RR of breast cancer RR (95% CI) 1.09 (1.04-1.13) for an increment of 10 g/day of alcohol 1.41 (1.18-1.69) for intake of 30 to < 60 g alcohol/day versus nondrinkers Alcohol intake was positively associated with breast cancer risk	reproductive and anthropometric factors did not change the association		Smith-Warner et al. (1997)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
retrospective cohort	654 cases among 96,565 U.S. health plan-members (1964-1972) > 15 years at enrollment and followed until 1977	**Evaluation:** participants completed questionnaire	**Estimation**: calculated adjusted RR of breast cancer RR 1.0 for 0 drinks/day 1.38 for 3+ drinks/day (p trend = 0.035)	controlled for age, body mass index, reproductive factors		Hiatt and Bawol (1984)
prospective cohort	303 cases among 69,000 U.S. health plan-members; five yr follow-up	**Evaluation:** participants completed questionnaire	**Estimation**: calculated adjusted RR of breast cancer RR (95% CI) 1.0 for 0 drinks/day 2.2 (1.2-3.9) for past drinkers 1.5 (1.0-2.3) for 1-2 drinks/day 1.5 (0.8-2.8) for 3-5 drinks/day 3.3 (1.2-9.3) for ≥ 6 drinks/day	controlled for age, race, smoking, body mass index, cholesterol, reproductive factors		Hiatt et al. (1987)
prospective cohort	121 cases among 7,188 U.S. females age 25-74 yr who participated in the First National Health and Nutrition Examination Survey (1971-1975); median follow up 10 yr	**Evaluation:** participants completed questionnaire	**Estimation**: calculated adjusted RR of breast cancer RR (95% CI) 1.0 for no drinks in past year 1.4 (0.8-2.5) for > 0.1-1.2 drinks/day 1.6 (0.9-3.1) for 1.3-4.9 drinks/day 2.0 (1.1-3.7) for ≥ 5 drinks/day	controlled for age, education, body mass index, dietary fat, reproductive factors		Schatzkin et al. (1987)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Laryngeal Cancer Case-Control Studies						
case-control	**Cases:** 326 laryngeal cancer patients **Controls:** 1134 matched by sex and age; approximately half of the controls reported drinking less than 100 g ethanol/wk	**Evaluation:** participants completed questionnaires	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI not given) 1.0 for 0-100 g/week 1.5 for 101-200 g/week 3.2 for 201-300 g/week 4.1 for 301+ g/week	RR adjusted for tobacco		Olsen et al. (1985)
case-control	**Cases:** 814 male laryngeal cancer patients **Controls:** 3057 males from general population	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI) Endolarynx (supraglottic) 1.0 for 0-20 g/day 0.88 (0.58-1.35) for 21-40 g/day 1.08 (0.74-1.58) for 41-80 g/day 1.68 (1.12-2.51) for 81-120 g/day 2.0 (1.33-3.02) for 121+ g/day Endolarynx (glottic and subglottic): 1.0 for 0-20 g/day 0.84 (0.49-1.44) for 21-40 g/day 1.05 (0.65-1.69) for 41-80 g/day 1.73 (1.05-2.86) for 81-120 g/day 3.40 (2.07-5.56) for 121+ g/day Epilarynx: 1.0 for 0-20 g/day 0.87 (0.29-2.65) for 21-40 g/day 1.53 (0.60-3.87) for 41-80 g/day 5.10 (2.09-12.44) for 81-120 g/day 10.64 (4.38-25.84) for 121+ g/day	RR adjusted for smoking, but adjustment did not affect crude RR		Tuyns et al. (1988)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 94 male laryngeal cancer patients **Controls:** 282 male patients not diagnosed with cancer or tobacco- and alcohol-related diseases; approximately half of the control group reported drinking <90 ml of alcohol per day	**Evaluation:** interviews	**Estimation:** calculated OR for laryngeal cancer based on alcohol consumption OR (95% CI) 1.0 for non-drinker 0.27 (0.10-0.72) for <90 mL/day 1.22 (0.60-2.48) for 90-180 mL/day 2.42 (1.18-4.93) for 180-360 mL/day 11.14 (3.84-32.37) for > 360 ml/day	adjusted for smoking		Choi and Kayho (1991)
case-control	**Cases:** 217 males with epilaryngeal cancer **Controls:** unknown number from national survey (~4000 males)	**Evaluation:** hospital chart records of alcohol and tobacco consumption compared to consumption by general population	**Estimation:** calculated RR for epilaryngeal cancer RR (95% CI) 1.0 for 0-39 g ethanol/day 1.9 (0.9-4.8) for 40-99 g ethanol/day 18.7 (8.1-42.9) for 100-159 g ethanol/day 101.4 (44-233.9) for 160+ g ethanol/day	RR adjusted for smoking The authors note that the controls may have underreported their alcohol consumption, leading to an overestimation of the RR for alcohol.	IARC (1988) noted that information on tobacco and alcohol use was obtained by different methods and in different interview situations for cases and controls	Brugere et al. (1986)
case-control	**Cases:** 832 male laryngeal cancer patients **Controls:** 1210 with cancers not reported to be related to alcohol or tobacco use; 23 of these did not have cancer	**Evaluation:** hospital admission records	**Estimation:** calculated OR for laryngeal cancer based on ethanol consumption OR (95% CI) 1.0 for 0 centiliters/wk 1.7 (1.0-3.2) for 1-35 cl/wk 1.8 (1.1-2.9) for 36-140 cl/wk 1.5 (0.8-2.9) for 141+ cl/wk	OR adjusted for smoking, age		Dosemeci et al. (1997)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 209 white male laryngeal cancer patients **Controls:** 209 matched for age, sex, hospital and educational/religious status; alcohol consumption was significantly lower than cases	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI) (1 unit = 9.5 g ethanol) 1.0 for never drank or < 1 unit/day of mainly straight whiskey 1.8 (0.9-3.2) for 1-6 units/day 5.3 (2.5-11.2) for 7+ units/day 1.8 (1.0-2.9) for beer or wine, irrespective of amount consumed	RR adjusted for smoking	IARC (1988) noted that some of the tumors classified as laryngeal might have been pharyngeal.	Wynder et al. (1956; cited by IARC, 1988)
case-control	**Cases:** 224 male laryngeal cancer patients **Controls:** 414 males matched by year of interview, hospital status and age at diagnosis	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (95% CI) 1.0 for < ~10 g/day 1.2 (0.8-1.9) for ~10-60 g/day 2.3 (1.5-3.4) for > 60 g/day	RR adjusted for smoking		Wynder et al. (1976; cited by IARC, 1988)
case-control	**Cases:** 184 male laryngeal cancer patients **Controls:** 184 males matched for age and area of residence	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption RR (90% CI) 4.4 (2.2-8.5) for <24 g/day 3.9 (2.1-7.3) for 24-58 g/day 4.8 (2.3-9.9) for > 60 g/day	RR adjusted for smoking		Burch et al. (1981; cited by IARC, 1988)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 154 males and females with laryngeal cancer **Controls:** 374 with other cancers	**Evaluation:** interviews	**Estimation:** calculated RR for laryngeal cancer based on alcohol consumption per week RR (95% not calculated) Extrinsic larynx: 1.0 for < 24 g 1.7 for 24-96 g 2.6 for 120-216 g 5.1 for 240-480 g 6.4 for > 480 g Intrinsic larynx 1.0 for < 24 g 1.1 for 24-96 g 0.7 for 120-216 g 2.0 for 240-480 g 2.2 for > 480 g	RR adjusted for smoking, socioeconomic group, marital status, dental care and history of tuberculosis		Elwood et al (1984; cited by IARC, 1988)
case-control	**Cases:** 365 male laryngeal cancer patients **Controls:** 1703 males	**Evaluation:** participants completed questionnaire	**Estimation:** calculated OR using unconditional multiple logistic regression for laryngeal cancer based on alcohol drinks (1 drink = 12 g of ethanol) per week OR (95% CI) 0.51 (0.27-0.96) for 1-13 0.35 (0.22-0.56) for 14-27 0.38 (0.24-0.61) for 28-41 0.76 (0.47-1.25) for 42-55 1.06 (0.68-1.65) for ≥ 56	RR adjusted for smoking		Franceschi et al. (1994)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Liver Cancer Case-Control Studies						
case-control	**Cases**: 265 males and females with histologically confirmed primary liver cancer in New Jersey Response = 89.5% **Controls**: 530 persons matched to cases by age, race, sex, and county of residence; selected from hospital in which the cases were diagnosed and excluding patients diagnosed with hepatitis, cirrhosis, or other liver disease Response = 77%	**Evaluation**: interviews; 96% of case interviews were proxy interviews with family members of the deceased cases	**Estimation**: calculated adjusted Mantel-Haenszel RR for liver cancer and level of alcohol consumption RR (95% CI; no. cases/no. controls) for males 1.00 for abstainers 1.01 (0.48-2.12; 59/155) for 0-4000 mL ethanol/yr 1.17 (0.51-2.70; 44/87) for 4000-16000 mL ethanol/yr 2.52 (0.97-6.54; 29/30) for 16000-33000 mL ethanol/yr 1.96 (0.75-5.10; 32/54) for > 33000 mL ethanol/yr RRs higher for females; dose-response trends by level of alcohol consumption significant ($p < 0.05$) for males and females	RR adjusted for age and smoking		Stemhagen et al. (1983)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 194 patients with confirmed hepatocellular carcinoma **Controls:** 456 patients in cancer or trauma hospitals with diseases other than neoplasm or liver disease	**Evaluation**: interviews	**Estimation**: calculated adjusted RR for hepatocellular carcinoma (HCC) using logistic regression RR for HCC with cirrhosis 1.0 for 0-9 g ethanol/day 0.7 for 10-39 g ethanol/day 1.0 for 40-69 g ethanol/day 1.2 for 70+ g ethanol/day RR for HCC without cirrhosis 1.0 for 0-9 g ethanol/day 0.8 for 10-39 g ethanol/day 0.9 for 40-69 g ethanol/day 0.8 for 70+ g ethanol/day	RR adjusted for age, sex, viral antibody status, and smoking		Trichopoulos et al. (1987)
case-control	**Cases:** 165 from several U.S. hospitals **Controls:** 465 from same hospital as cases, excluding individuals with current diagnosis of tobacco and alcohol-related cancers	**Evaluation:** interviews	**Estimation**: calculated adjusted OR using logistic regression OR for males > 50 yr 1.00 for 0-1drinks/day 1.13 for 1-2 drinks/day 1.38 for > 3 drinks/day OR for females > 50 yr 1.00 for 0-1 drinks/day 1.87 for 1-2 drinks/day 3.48 for > 3 drinks/day test for trend in females statistically significant ($p < 0.05$)	OR adjusted for age at diagnosis, ethnic group, education, occupation, and religion		Yu et al. (1988)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases**: 187 Japanese males with newly diagnosed liver cancer **Controls**: 192 Japanese males admitted to gastroenterology clinics for checkups, without liver or alcohol-related diseases and age-matched to cases	**Evaluation:** interviews	**Estimation**: calculated adjusted RR for liver cancer using logistic regression RR (95 % CI) 1.0 for 0-2.7 x 10^5 mL total ethanol consumed (sake; referent) 1.0 (0.6-1.6) for 2.7 x 10^5 - 1.08 x 10^6 mL total ethanol consumed (sake) 2.2 (1.2-4.0) for $\geq$ 1.08 x 10^6 mL total ethanol consumed (sake) positive trend ($p = 0.0273$)	RR adjusted for age, HBsAg, history of blood transfusion, cigarette index, and family history of liver cancer		Tsukuma et al. (1990)
case-control	**Cases**: 204 Japanese patients diagnosed with hepatocellular carcinoma **Controls**: 410 persons without chronic liver disease in same region as cases who visited a public health center; matched to cases by sex and age	**Evaluation:** interviews	**Estimation:** calculated adjusted RR of hepatocellular carcinoma using logistic regression RR (95% CI) for males and females 1.0 for non-drinker (referent) 1.0 (0.6-1.7) for cumulative alcohol intake of 0.1-33.9 drink-years 1.1 (0.6-1.8) for cumulative alcohol intake of 34.0-76.6 drink-years 1.9 (1.1-1.3) for cumulative alcohol intake of 76.7+ drink-years drink-years categorized by quartiles among male controls positive trend ($p = 0.01$)	RR adjusted for sex, age; adjustment for HBsAg did not significantly change the estimates		Tanaka et al. (1992)
case-control	**Cases**: 83 males deceased from hepatocellular carcinoma and 15 males deceased from cholangiocarcinoma; identified through Swedish cancer registry **Controls**: two deceased population controls identified for each case in the National Population Register	**Evaluation:** relatives completed questionnaires; categorized cases into nondrinkers, light , moderate, heavy consumers of spirits	**Estimation:** calculated RR for hepatocellular carcinoma RR (95% CI) 1.0 for nondrinkers 2.1 (0.9-5.1) for light drinkers 2.9 (.99-8.7) for moderate drinkers 4.3 (1.8-10.8) for heavy drinkers		IARC(1988) noted: no hepatitis B serology	Hardell et al. (1984)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases**: 60 males and 26 females in five U.S. states diagnosed with liver cancer **Controls**: 110 males and 51 females; hospital patients without primary liver disease matched to cases by age, sex, and race	**Evaluation**: interviews	**Estimation**: calculated matched RR for liver cancer RR 1.0 for nondrinkers 1.4 for infrequent drinkers 2.3 for occasional drinkers 2.6 for regular drinkers (at least once/day) statistically significant trend test increased RRs for alcohol use after adjustment for smoking	gender, age, race, smoking		Austin et al. (1986)
case-control	**Cases**: 61 males in France with primary liver cancer **Controls**: 61 males admitted to hospitals for trauma; age-, sex-, and interviewer- matched to cases	**Evaluation:** personal interviews; obtained drinking history to 10 yr prior to interview; cases and controls reported equal ethanol intake	High, but equal, alcohol consumption among cases and controls.		IARC (1988) noted high but equal alcohol consumption among cases and controls	Schwartz et al. (1962; cited by IARC,1988)
case-control	**Cases**: 95 males and 12 females in Hong Kong with histologically confirmed primary liver cancer **Controls**: 94 males and 13 females matched to cases for age, sex, and hospital in Hong Kong	**Evaluation**: personal interviews; obtained socioeconomic status, birthplace, HBV exposure, dietary history and habits	**Estimation**: no data reported but the authors stated no significant positive association between liver cancer and alcohol intake			Lam et al. (1982)
case-control	**Cases**: 74 males and 16 females diagnosed with primary liver cancer **Controls**: 74 male and 16 female hospital patients with normal liver function age- and sex-matched to cases	**Evaluation:** categorization into 'heavy' and 'light' drinkers using mean ethanol intake per day heavy/light aflatoxin load per day was estimated by food items consumed	**Estimation:** calculated matched RR for liver cancer from combined effects of aflatoxin load and alcohol intake: RR 1.0 for light aflatoxin, light alcohol 3.9 ($p \leq 0.05$) for light aflatoxin, heavy alcohol 17.5 ($p = 0.05$) for heavy aflatoxin, light alcohol 35.0 ($p = 0.05$) for heavy aflatoxin, heavy alcohol	age, sex, hepatitis B infection	IARC (1988) noted interpretation is limited by lack of hepatitis B serology	Bulatao-Jayme et al. (1982)

Table 3-1. Human Studies of Alcohol (Continued)

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
Liver cancer cohort studies						
cohort	5135 Japanese doctors followed 1965-1983	**Evaluation:** self-administered questionnaire in 1965	**Estimation**: calculated adjusted RR for death from liver cancer (19 yr follow-up) RR (95% CI) 1.4 (0.4-4.8) for ex-drinkers 1.5 (0.6-3.8) for occasional drinkers 2.0 (0.8-5.1) for daily drinkers of < 2 go of sake 2.7 (1.0-6.8) for daily drinkers of > 2 go of sake	RR adjusted for age and smoking but not hepatitis B infection	IARC (1988) noted no data on hepatitis B virus serology	Kono et al. (1986)
cohort	Danish Brewery workers cohort		**Estimation**: calculated RR for liver cancer RR; no. observed/no. expected 1.5; 29/19.2, significant			Jensen (1980; cited by IARC, 1988)
cohort	Finnish alcohol misusers 1944-1959 (205000) and alcoholics 1967-1970 (4370) cohorts; linked with Finnish cancer registry 1965-1970		**Estimation:** calculated RR for liver cancer RR; no. observed/no. expected 1.5; 66/44.3, $p < 0.05$ for alcohol misusers 2.5; 2/0.77, not significant for alcoholics	age		Hakulinen et al. (1974)
cohort	Japanese population; follow-up of 639 males in fishing area and 677 males in farming area; followed from 1958-1980	**Evaluation:** interviews at initiation of follow-up	**Estimation**: calculated SMR for death from liver cancer SMR Fishing Area Men 5.7 ($p < 0.001$) for < 1 units shochu 7.5 ($p < 0.001$) for 1-2 units shochu 20 ($p < 0.001$) for > 2 units shochu no effect of sake or shochu drinking on men in farming area, and no effect of sake drinking on men in fishing area	age, hepatitis B infection	IARC(1988) noted no data on hepatitis B virus serology	Shibata et al. (1986)

Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; CI = confidence interval

4.0 EXPERIMENTAL CARCINOGENESIS

4.1 Studies Reviewed by IARC (1988)

One study reported no increased tumor incidence in rats administered alternating doses of pure ethanol in water (15% and 55%), farm apple brandy (15% and 55%), or industrial apple brandy (15% and 40%) as the drinking fluid for up to 23 mo. The higher concentrations were supplied on alternate days and controls were exposed to water alone. Other animal studies were considered inadequate for evaluation of carcinogenic effects of ethanol.

A number of adequate studies reported the tumor incidence in animals given ethanol in combination with a known carcinogen. Mice orally administered ethanol and *N*-nitrosodimethylamine (NDMA) had an increased incidence of nasal cavity tumors. Ethanol also enhanced the incidence of esophageal/forestomach tumors and lung tumors in mice given *N*-nitroso-diethylamine (NDEA) or *N*-nitrosodi-*n*-propylamine by oral administration. The incidence of benign tumors in the nasal cavity of rats was enhanced by ethanol administered in a liquid diet with *N'*-nitrosonornicotine. In addition, hamsters given *N*-nitrosopyrrolidine (NPyr) by intraperitoneal (i.p.) injection showed a higher incidence of nasal cavity and tracheal tumors and neoplastic liver nodules if ethanol was simultaneously administered. Rats exposed to vinyl chloride via inhalation had a higher incidence of liver tumors when ethanol was administered in the drinking water.

IARC (1988) concluded that there is inadequate evidence for the carcinogenicity of ethanol and alcoholic beverages in experimental animals. Earlier review groups (IARC, 1985, 1987) concluded that there is sufficient evidence for the carcinogenicity of acetaldehyde (the initial metabolite of ethanol) in experimental animals.

4.2 Studies Post-IARC (1988)

All tumor incidences are presented in ascending order from control to highest dose.

4.2.1 Mice

One recent study examined the effects of ethanol on mammary carcinogenesis (Hackney et al., 1992). The strain of mice treated have a high spontaneous mammary tumor incidence, but the mammary tumorigenesis was not enhanced by ethanol administered in drinking water, by gavage, or as part of a liquid diet. Groups were given ethanol at a rate of 15 g/kg/day in drinking water, 4 g/kg/day by gavage, or 20 g/kg/day in a defined diet. Compared to isocaloric controls, treatment groups showed either no change or a decrease in tumor incidence (Hackney et al., 1992).

Two other studies with mice provide evidence that coexposure to nitrosamines and ethanol potentiates the carcinogenicity of nitrosamines. In one study (Anderson et al., 1992), the incidence of lung tumors was significantly ($p<0.05$) greater in groups given NDMA (5 ppm) + ethanol (1%, 5%, or 10%) in drinking water than in a group given only NDMA (27/50, 47/49, 46/48, 49/50). A statistically significant increase in lung tumors was seen in mice exposed to NDMA (1 ppm) and 10% ethanol in drinking water for 48 or 72 wk and in mice given an intragastric (i.g.) dose of NDMA administered with an ethanol (5%, 10%, or 20%) solution.

Another coexposure study (Anderson et al., 1993) extended the nitrosamine exposure to include NDEA, NPyr, and N^6 - (methylnitroso) adenosine (MNAR). The NDEA + ethanol group had a significantly ($p<0.01$) greater lung tumor multiplicity than the NDEA only group (5.8, 1.5). The incidence of forestomach tumors was also greater in the NDEA + ethanol group than in the NDEA-only group (16/50, 1/50). In addition, the NPyr + ethanol groups showed a significant ($p<0.01$) increase in the incidence of lung tumors compared to the NPyr- only groups, at 6.8 ppm NPyr (33/49, 20/49) and 40 ppm NPyr (47/48, 22/49). At the high dose of MNAR, the incidence of thymic lymphoma was significantly increased in the MNAR + ethanol group compared to the group treated with MNAR only (32/50, 21/49).

4.2.2 Rats

A study explored cancer metastasis in rats given ethanol prior to and during development of a primary tumor (Yirmiya et al., 1992). Rats were administered ethanol in a liquid diet followed by lung cancer induction by injection of murine lymphoma cells. The ethanol exposed group had significantly ($p<0.05$) more metastases, indicated by cell morphology, than control groups given a standard liquid or solid diet.

The influence of ethanol on the initiation stage of cancer induction by nitrosamines was investigated in several studies. In one study (Grubbs et al., 1988), rats were gavaged with two doses of ethanol and weeks later given dimethyl benzanthracene (DMBA) or methylnitrosourea (MNU). Ethanol-pretreated groups had a greater number of mammary cancers per rat after treatment with DMBA than groups not pretreated (high dose 5.6; low dose 5.4; sucrose 4.0; none 3.4).

Three studies examined mammary tumors in rats exposed to ethanol before, during and after treatment with DMBA or MNU. In one study (Singletary et al., 1991), groups were fed diets with ethanol as a percentage of calories before, and seven days after, treatment with DMBA, or only after DMBA treatment. Compared to the control group, the incidence of mammary tumors was significantly ($p<0.05$) greater in rats fed 20% ethanol before and after dosing with DMBA (47%, 82%). Likewise, in comparison to the control group, the incidence of mammary tumors in rats fed 15% ethanol was significantly ($p<0.05$) greater (49%, 83%). There was no significant difference, however, in the incidence of rats with mammary tumors from the group given 30% ethanol and the controls.

A similar study investigated dietary ethanol and the carcinogen MNU (Singletary et al., 1995). Groups were fed diets with ethanol as a percentage of calories before, during and seven days after treatment with MNU, or only after MNU treatment. There was a significant ($p<0.05$) difference in mammary tumor incidence between the 15% ethanol group and the control group, but there was no significant difference in the mammary tumor incidence between rats given 20% or 30% ethanol and the controls. A significant ($p<0.05$) difference in mammary adenocarcinomas per rat and in final palpable tumor number per rat was also observed between the 15% ethanol group and the control group. In addition, the 20% ethanol group had a significantly higher final palpable tumor incidence compared to the controls.

Finally, ethanol had no effect on mammary tumor incidence in rats given ethanol as a dietary caloric percentage before, during, and after treatment with DMBA (Rogers and Connor, 1990). A group was administered 10% of their calories as ethanol at age 24-28 days, 20% of their calories as ethanol at age 28-230 days, and DMBA (20 mg/kg) by gavage at age 55 days. In the control group, fat was substituted for ethanol.

Another study that investigated the incidence of DMBA-induced mammary tumors in rats pretreated with ethanol did not find that ethanol potentiated tumor incidence (McDermott et al., 1992). Animals were administered ethanol (5%) in the drinking water from age 40 to 50 days and given an i.g. dose of DMBA (15 mg) at age 50 days. At age 116 days, the incidence of mammary tumors was greater in the control than in the treated group (18/18, 8/20).

Several studies examined tumor incidence in rats coexposed to a nitrosamine and ethanol. Cotreatment of rats with diethyl nitrosamine (DEN) and ethanol in drinking water resulted in an increase of esophageal tumors compared to tumors after exposure to only DEN (Aze et al., 1993). Groups were administered two doses of DEN (33 ppm, 50 ppm) or one dose of DEN (50 ppm) and ethanol (10%) in drinking water. The group coexposed to DEN and ethanol had a significant ($p<0.01$) number of rats with esophageal papilloma (1/26, 2/28, 10/26), esophageal carcinoma (0/26, 1/28, 8/26), and esophageal papilloma and carcinoma combined (1/26, 3/28, 15/26), compared to groups exposed to both levels of DEN alone.

Yamagiwa et al. (1991, 1994) investigated liver cancer in male and female rats simultaneously exposed to female hormones and ethanol. Groups were given by stomach tube ethynylestradiol (EE; 0.075 mg) and norethindrone acetate (NA; 6.0 mg) with and without ethanol (10%) in drinking water; liver examinations were made every two wk for 12 mo. The incidence of hepatocellular carcinoma was significantly ($p<0.05$) elevated at 12 mo. in females treated with NA, EE and ethanol compared to females treated with NA and EE only (2/25, 9/22). This increase in hepatocellular carcinoma was not seen in the males rats in the study.

In contrast, the incidence of glandular stomach carcinoma and duodenal carcinoma was significantly reduced in rats coadministered ethanol with the nitrosamine *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in a drinking solution, compared to tumor induction by MNNG given without ethanol (Cerar and Pokorn, 1996). Groups of rats were given MNNG (100 µg/mL) in tap water, MNNG (100 µg/mL) in 11% ethanol, or MNNG (100 µg/mL) in wine. The solutions were administered for six mo followed by a normal diet until study termination at mo 13. The glandular stomach adenocarcinoma incidence in the group treated with only MNNG was significantly ($p=0.037$) increased compared to groups given MNNG in wine or in an ethanol solution (6/17, 1/18, 1/19). An analogous conclusion was drawn concerning duodenal adenocarcinoma (4/17, 0/18, 0/19; $p < 0.0005$).

In one study, rats were coexposed to ethanol and methyl-*n*-amylnitrosamine (MNAN) and then administered ethanol for life (Mirvish et al., 1994). Groups were given three i.p. injections of MNAN; one group was simultaneously administered ethanol in drinking water, which continued throughout the animals' lives. Histological examinations showed no change in the incidence of tumors in the esophagus, nasal cavity, tongue, forestomach, and thyroid between groups treated with MNAN and MNAN + ethanol.

4.2.3 Hamsters

A study with hamsters investigated cancer in the offspring of pregnant females exposed to ethanol early in gestation and later given the nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Schuller et al., 1993). Offspring of the group transplacentally exposed to NNK and ethanol had a significantly ($p<0.01$) greater overall tumor incidence than both offspring exposed to NNK only and offspring of the control group (M: 8/16, 3/9, 0/12; F: 13/17, 6/15, 0/16).

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Mice							
6-wk-old C3H/Ou mice; (strain known to develop mammary cancer spontaneously)	Expt I: 15 F Expt II: 10 F Expt III: 14 F	Expt I: 15 F Expt II: 16 F Expt III: 20 F	ethanol USP 95%	Expt I: semipurified solid diet and 15 g/kg/day ethanol in drinking water Expt II: isocaloric pair feeding semipurified diet and 4 g/kg/day ethanol by gavage five times per wk Expt III: isocaloric pair feeding of Lieber-DeCarli liquid diet and 20 g/kg/day ethanol in diet	65 wk	Expt I: rate of mammary tumor development delayed in treated group so the median incidence was 17 wk later than controls ($p=0.03$); control mice gained weight more rapidly and consumed more calories from solid food but both groups consumed approximately equal total daily calories Expt II: rate of mammary tumor development, weight gain, and calorie consumption similar in treated and control groups Expt III: no significant ($p=0.10$) difference in rate of mammary tumor development; weight gain same in both groups for 14 wk and then decreased in treated group	Hackney et al. (1992)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
4-6-wk old A/JNCr mice	Expt I: four groups of 50 M Expt II: 12 groups of 50 M Expt III: nine groups of 30 M Expt IV: five groups of 25 M	Expt I: two groups of 25 M Expt II: four groups of 50 M Expt III: three groups of 30 M Expt IV: five groups of 25 M	ethanol; reagent grade NDMA (*N*-nitrosodimethylamine) technical grade	Expt I: groups given 0 or 5 ppm NDMA in drinking water and 0, 1, 5, or 10% ethanol in drinking water Expt II: groups given 1 ppm NDMA in drinking water and 0 or 10% ethanol in drinking water Expt III: groups given 0, 1, or 5 mg/kg NDMA single i.g. dose administered with 0, 5, 10, or 20% ethanol Expt IV: groups given 0 or 1 mg/kg NDMA by various routes (i.g., i.p., s.c., i.v.) and 0 or 10% ethanol in drinking water	Expt I: 4 wk then held 12 wk Expt II: 16, 32, 48, or 72 wk Expt III: 16 wk Expt IV: NDMA 5 x/wk for 4 wk; animal sacrifice at 32 wk	Expt I: the incidence of lung tumors was significantly ($p<0.05$) greater in all groups given NDMA + ethanol than in the group given NDMA only: NDMA + ethanol 0% 1% 5% 10% 27/50 47/49 46/48 49/50 Expt II: after 48 and 72 wk, the incidence of lung tumors was significantly ($p<0.05$) greater in groups given NDMA + ethanol than in the group given NDMA only: NDMA NDMA + ethanol 48 wks 32/48 45/49 72 wks 42/48 48/49 Expt III: the incidence of lung tumors was significantly ($p<0.05$) greater with 5 mg/kg NDMA + ethanol at all concentrations than in the group given NDMA only: NDMA + ethanol 0% 5% 10% 20% 15/30 27/30 30/30 30/30 Expt IV: no significant effects of ethanol with repeated doses of 1 mg NDMA/kg	Anderson et al. (1992)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Expt I: 4-wk-old A/JNCr mice Expt II: 4-wk-old Swiss (NIH:Cr(S)) mice	Expt I: six groups of 50 M; one group of 25 M Expt II: five groups of 50 F	Expt I: one group of 25 M Expt II: one group of 50 F	ethanol; reagent grade NDEA (*N*-nitrosodiethylamine); analytical grade Npyr (*N*-nitrosopyrrolidine); analytical grade MNAR (N^6-(methylnitroso)adenosine; synthesized; purity n.p.	Expt I: groups given 0 or 6.8 ppm NDEA or 0, 6.8 or 40 ppm NPyr and 0 or 10% ethanol in sterilized distilled drinking water Expt II: groups given i.g. doses of 0, 60, or 120 mg MNAR/kg and 0 or 15% ethanol	Expt I: 4 wk; mice held 32 wk Expt II: three doses per wk for 12 wk; mice sacrificed when ill or at age 18 mo	Expt I: The NDEA-treated group showed a significant ($p < 0.01$) increase in lung tumors compared to untreated controls (42/50, 9/24). The NDEA + ethanol group had a significantly ($p<0.01$) greater lung tumor multiplicity than the NDEA group (5.8, 1.5). The incidence of forestomach tumors was also greater in the NDEA + ethanol group than in the NDEA only group (16/50, 1/50). The NPyr + ethanol groups showed a significant ($p<0.01$) increase in the incidence of lung tumors compared to the NPyr only groups at 6.8 ppm NPyr (33/49, 20/49) and 40 ppm NPyr (47/48, 22/49). However, the lung tumor incidence in the low dose NPyr + ethanol group was not significantly different from the incidence in the ethanol only group, so definitive interpretation is not possible. Expt II: Coexposure to ethanol significantly reduced survival time at the lower dose of MNAR. At the high dose of MNAR, the incidence of thymic lymphoma was significantly increased in the MNAR + ethanol group compared to the group treated with MNAR only (21/49, 32/50).	Anderson et al. (1993)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Rats							
10-12-wk old Fischer 344 rats	one group of 9 or 10 M	two groups of 9-10 M	ethanol; purity n.p.	Treated group received a liquid diet with ethanol as 5% w/v and 35% ethanol-derived calories. Control groups received an isocaloric diet (pair-feeding) or normal rat chow and water. All groups were inoculated with murine lymphoma cells.	Lungs were removed and examined 3 wk after inoculation.	Ethanol-exposed rats had significantly ($p<0.05$) more metastases than both control groups.	Yirmiya et al. (1992)
35-day-old Sprague-Dawley rats	Expt I and Expt II: four groups of F; no. n.p.	Expt I and Expt II: one group of F; no. n.p.	ethanol; purity n.p. Expt I: DMBA (dimethylbenzanthracene); purity n.p. Expt II: MNU (methylnitrosourea); purity n.p.	Expt I: groups given two gavage doses of ethanol (3.5 g/kg; 7.0 g/kg); sucrose (isocaloric to the high dose of ethanol); or no treatment; then DMBA (10 mg) Expt II: ethanol treatment as above; MNU (50 mg/kg) by i.v.	Expt I: ethanol treatment for 3 wk; DMBA at age 58 days for 6 mo Expt II: ethanol treatment for 8 wk; MNU at age 93 days for 7 mo	Expt I: Both ethanol pretreated groups had a greater no. of mammary cancers per rat after treatment with DMBA than groups not pretreated (high dose-5.6; low dose-5.4; sucrose-4.0; none-3.4); statistical analyses n.p. Expt II: The group pretreated with the high dose of ethanol had a greater no. of mammary cancers per rat after treatment with MNU than groups not pretreated (hi dose-2.5; low dose-2.0; sucrose-1.7; none-2.0); statistical analyses n.p.	Grubbs et al. (1988)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Expt I and II: 21-22-day-old Sprague-Dawley rats Expt III: 42-day-old Sprague-Dawley rats	Expt I: one group of 17 F Expt II: two groups of 26 and 31 F Expt III: two groups of 30 and 31 F	Expt I: one group of 15 F Expt II: one group of 33 F Expt III: one group of 31 F	ethanol; 95% purity DMBA; purity n.p.	Expt I: groups given a liquid diet; then given diets with ethanol at 0% or 20% of calories; i.g. administration of DMBA (30 mg/kg) Expt II: groups given a liquid diet; then given diets with ethanol at 0%, 10%, or 20% of calories; i.g. administration of DMBA (35.7 mg/kg) Expt III: groups given powdered control diet; administered DMBA (32.3 mg/kg); groups then given diets with ethanol at 0%, 15%, or 30% of calories	Expt I: liquid control diet to age 30 days; ethanol diet at age 30-57 days; DMBA at age 58 days; ethanol diet at age 58-65 days; powdered diet at age 65-78 days Expt II: liquid control diet to age 25 days; ethanol diet at age 25-52 days; DMBA at age 53 days; ethanol diet at age 53-60 days; powdered diet at age 60-79 days Expt III: powdered diet at age 42-56 days; DMBA at age 56 days; ethanol at age 63-203 days	Expt I: Compared to the control group, the incidence of mammary tumors was significantly ($p<0.05$) greater in rats fed 20% ethanol (47%, 82% respectively). Expt II: Compared to the control group, the incidence of mammary tumors was significantly ($p < 0.05$) greater in rats fed 20% ethanol (48%, 74% respectively), but there was no significant difference in the incidence of rats with mammary tumors between the low ethanol dose group and controls. On diets containing 0%, 10%, and 20% calories as ethanol, the incidence of tumor-bearing rats having adenocarcinomas was 78%, 82%, and 91%, respectively. Expt III: Compared to the control group, the incidence of mammary tumors was significantly ($p < 0.05$) greater in rats fed 15% ethanol (49%, 83% respectively), but there was no significant difference in the incidence of rats with mammary tumors in the group given 30% ethanol versus controls. On diets containing 0%, 15%, and 30% calories as ethanol, the incidence of tumor-bearing rats having adenocarcinomas was 74%, 93%, and 90%, respectively.	Singletary et al. (1991)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
Expt I: 23-day-old Sprague-Dawley rats Expt II: 38-day-old Sprague-Dawley rats	Expt I: three groups of 32 F Expt II: four groups of 32, 30, 30, and 30 F	Expt I: three groups of 32 F each Expt II: two groups of 32 F each	ethanol; purity 95% MNU; purity n.p.	Expt I: groups given a powdered diet; then given diets with ethanol at 0%, 15%, 20% or 30% of calories; then i.p. administration of MNU (30 mg/kg); then ethanol diet; then powdered diet Expt II: groups given powdered control diet; administered MNU (30 mg/kg); groups then given diets with ethanol at 0%, 15%, 20%, or 30% of calories	Expt I: powdered control diet to age 28 days; ethanol diet at age 28-49 days; MNU at age 50 days; ethanol diet at age 50-57 days; powdered control diet at age 57-72 days Expt II: powdered diet at age 38-51 days; MNU at age 51 days; ethanol diet at age 58-73 days	Expt I: Significant ($p<0.05$) difference in mammary tumor incidence between the control group (59%) and the 15% ethanol group (75%), but no significant difference in the mammary tumor incidence between controls and the group given 20% ethanol (66%) or in the group given 30% ethanol (69%). Expt II: Significant ($p<0.05$) difference in mammary adenocarcinomas per rat and in final palpable tumor no. per rat between 15% ethanol group and control group. The 20% ethanol group also had a statistically significant increased final palpable tumor incidence compared to controls, but there was no significant difference in the mammary tumor incidence between rats given 30% ethanol and controls.	Singletary et al. (1995)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
21-day-old Sprague-Dawley rats	two groups of 50 F	one group of 50 F	ethanol; purity n.p. DMBA; purity n.p.	Group 1: DMBA (20 mg/kg) by gavage and liquid diet with 20% calories as fat Group 2: DMBA (20 mg/kg) by gavage and liquid diet with 20% calories as fat; then 10% calories as ethanol; then 20% calories as ethanol Group 3: DMBA (20 mg/kg) by gavage and liquid diet with 20% calories as fat; then 10% calories as fat; then 20% calories as fat	Group 1: Rats at age 21-230 days Group 2: Rats given 20% calories as fat at 21-24 days of age, 10% calories as ethanol at age 24-28 days and 20% calories as ethanol at age 28-230 days Group 3: Rats given 20% calories as fat at 21-24 days of age, 10% calories as fat at age 24-28 days; 20% calories as fat at age 28-230 days DMBA in all groups at age 55 days	No significant difference in mammary tumors between groups	Rogers and Conner (1990)
40-day-old Sprague-Dawley rats	one group of 20 F	one group of 20 F	ethanol; lab grade DMBA; analytical purity	Group 1: ethanol (5%) in drinking water; then DMBA (15 mg) in sesame oil (1 mL) by i.g. Group 2: tap water; then DMBA (15 mg) in sesame oil (1 mL) by i.g.	Group 1: ethanol age 40-50 days Group 2: DMBA age 50 days diet and liquid age 50-170 days	Mammary tumors were reported in 100% of controls versus 40% of rats in the treated group ($p<0.001$) at age 116 days.	McDermott et al. (1992)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
5-wk-old Fischer 344 rats	Group 1: n=3 Group 2: n=30 Group 3: n=28 Group 4: n=30 All rats in study were male.	groups 2-4 controls for group 1	ethanol; purity > 99% DEN (diethylnitrosoamine); purity > 99%	Group 1: DEN (50 ppm) plus 10% ethanol in drinking water; then tap water Group 2: DEN (33 ppm) in drinking water; then tap water Group 3: DEN (50 ppm) in drinking water; then tap water Group 4: ethanol (10%) in drinking water; then tap water	Groups 1-4 treatment 8 wk; tap water 96 wk	Survival reduced at 104 wk in Group 1 (13%), Group 2 (57%), Group 3 (36%), and Group 4 (80%) Esophagus: Group 1 had a significant ($p < 0.01$) number of rats with papilloma, carcinoma, and papilloma and carcinoma combined compared to Groups 2 and 3. No tumor incidence in Group 4 given ethanol in drinking water without DEN: Papill. Carcin. Papill. + Carcin. Group 1 10/26 8/26 15/26 Group 2 1/26 0/26 1/26 Group 3 2/28 1/28 3/28 Group 4 0/28 0/28 0/28 Other tissues not examined.	Aze et al. (1993)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
4-wk-old Wistar JCL rats	Group 1: n=32 (5, 5, 5, 5, 12) Group 2: n=40 (5, 4, 5, 5, 21) Group 3: n=30 (5, 5, 5, 5, 10) Each group was subdivided for different treatment periods. All rats in the study were female.	Group 4: n=25 (5, 5, 5, 5, 5)	ethanol, EE (ethynyl estradiol); NA (norethinodrone acetate); all analytical purity	Group 1: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube Group 2: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 3: olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 4: olive oil (0.5 mL) by stomach tube	groups treated for 2, 4, 6, 8, and 12 mo EE and NA administered daily; ethanol given 5/7 days per wk, pure water given in remaining two days per wk	The incidence of hepatocellular carcinoma was significantly ($p<0.05$) elevated at 12 mo in Group 2 treated with NA, EE and ethanol compared to Group 1 treated with EE and NA (8/21, 1/12 respectively). No hepatocellular carcinomas developed in Groups 3 and 4 during the study.	Yamagiwa et al. (1991)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
4-wk-old Wistar rats	Group 1: n=45 F (5, 5, 5, 5, 25) and 36M (4, 4, 4, 4, 20) Group 2: n=41 F (5, 4, 5, 5, 22) and 33M (4, 4, 4, 4, 17) Group 3: n= 30 F (5, 5, 5, 5, 10) and 24 M (4, 4, 4, 4, 8) Each group was subdivided for different treatment periods.	one group of 25 F (5, 5, 5, 5, 5) one group of 20 M (4, 4, 4, 4, 4)	ethanol, EE, NA; all analytical purity	Group 1: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube Group 2: EE (0.075 mg) and NA (6.0 mg) in olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 3: olive oil (0.5 mL) by stomach tube plus ethanol (10%) in drinking water Group 4: olive oil (0.5 mL) by stomach tube	groups treated for 2, 4, 6, 8, and 12 mo EE and NA administered daily; ethanol given 5/7 days per wk, pure water given in remaining 2 days per wk	The incidence of hepatocellular carcinoma was significantly ($p<0.05$) elevated at 12 mo in the female group (Group 2) treated with NA, EE and ethanol compared to females in the group (Group 1) treated with NA and EE (9/22, 2/25). Males did not develop hepatocellular carcinoma except at 12 mo. in the group (Group 2) treated with NA, EE, and ethanol (2/17).	Yamagiwa et al. (1994)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
age n.p. Wistar rats	two groups of 20 M	one group of 20 M	MNNG (*N*-methyl-*N*-nitro-*N*-nitrosoguanidine), purity n.p.	Group 1: MNNG (100 µg/mL) in tap water Group 2: MNNG (100 µg/mL) in wine Group 3: MNNG (100 µg/mL) in 11% ethanol water solution one group for each treatment all solutions were administered as drinking fluid	0-6 mo for Group 1 0-6 mo plus 10 d for Groups 2-3 to equalize total MNNG consumption (Groups 2 and 3 consumed less liquid over 6 mo than Group 1) 6-13 mo only tap water for Group 1 6 mo plus 10 days-13 mo. only tap water for Groups 2-3	10% died before study termination at 13 mo: 3 in Group1, 2 in Group 2, 1 in Group 3. All organs except those in the central nervous system and skeleton were examined macroscopically. Glandular stomach: the adenocarcinoma incidence in Group 1 (6) was significantly (p=0.037) increased compared to Group 2 (1) and Group 3 (1); one sarcoma was found in Group 2. In the forestomach, the incidence of papilloma was not significantly different between groups - Group1 (1), Group 2 (0), Group 3 (1). Carcinoma of the forestomach was also identified in Group 1 (1), Group 2 (1), and Group 3 (2), but the difference was not significant. Duodenum: adenocarcinoma incidence in Group 1 (4) significantly ($p < 0.0005$) increased compared to Group 2 (0) and Group 3 (0)	Cerar and Pokorn (1996)

Table 4-1. Experimental Carcinogenicity Studies with Alcohol (Post-IARC, 1988) (Continued)

Age, Strain, Species	No. and Sex Exposed	No. and Sex Controls	Chemical Form and Purity	Dose and Route	Duration of Exposure	Results/Comments	Reference
6-wk-old MRC-Wistar rats	two groups of 40 and 25 M	one group of 10 M	ethanol; purity 95% MNAN (methyl-*n*-amylnitrosoamine); purity n.p.	Group 1: MNAN (25 mg/kg) by i.p. three times Group 2: MNAN (25 mg/kg) by i.p. three times and ethanol (20%) in drinking (distilled) water; then MNAN single i.p. (25 mg/kg) and ethanol (10%) in drinking water	Group 1: injection at 7, 8, 9 wk of age Group 2: injection of MNAN at age 7, 8 and 9 wks; ethanol (20%) continuously from age 6-8 wks; ethanol (10%) continuously from age 8-10 wks; then 5 days/wk for life	No significant difference in incidence of tumors in esophagus, nasal cavity, tongue, forestomach, and thyroid between group treated with MNAN and group treated with MNAN + ethanol	Mirvish et al. (1994)
Hamsters							
age n.p. Syrian golden hamsters	three groups of 4 pregnant F	4 F	ethanol; purity n.p. NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone); purity > 98%	Group 1: ethanol (10%) in drinking water Group 2: NNK (50 mg/kg) in distilled water by intratracheal instillation Group 3: ethanol in drinking water; NNK by intratracheal instillation control group given distilled water	Group 1: gestation days 5-16 Group 2: gestation day 15 Group 3: ethanol: gestation days 5-16; NNK: gestation day 15	survival similar between groups Offspring of the group transplacentally exposed to NNK and ethanol had a significantly ($p < 0.01$) greater overall tumor incidence (50% in males, 77% in females) than offspring exposed to NNK alone (33% in males, 40% in females) or offspring exposed to ethanol alone (5.9% in males, 4.3% in females). No control group offspring developed tumors during the study. A majority (10/17) of female offspring of the group treated with NNK and ethanol developed pancreatic tumors while female offspring of other treated groups developed no pancreatic tumors during the study.	Schuller et al. (1993)

5.0 GENOTOXICITY

Studies of the genotoxic effects of ethanol and alcoholic beverages published prior to 1988 have been reviewed by IARC (1988, pp. 135-159, see Appendix B). More recent studies are summarized in Section 5.2.

5.1 Genotoxicity Studies Reviewed by IARC (1988)

The peripheral blood lymphocytes of alcoholics showed increased frequencies of chromosomal aberrations when compared to nonalcoholics in studies that controlled for age, sex, duration of dependence, and smoking. Smoking alcoholics had a higher frequency of exchange-type aberrations than nonsmoking alcoholics. These aberration frequencies were also positively correlated to duration of alcohol dependence. Similar studies of sister chromatid exchange (SCE) or aneuploidy often did not control for confounding factors.

In rodents exposed to ethanol *in vivo*, inconsistent results were reported for chromosomal aberrations and SCE. Chromosomal aberrations were not induced in rats or hamsters, but one study showed chromosomal aberrations in rat embryos exposed *in vivo*. An increase in SCE was induced in mouse (but not hamster) bone-marrow, mouse embryo liver cells, and in rat peripheral blood lymphocytes exposed *in vivo*.

A high incidence of aneuploidy was seen in the fertilized eggs of female mice given ethanol after the predicted time of ovulation. Conflicting results were reported for induction of micronuclei and dominant lethal mutations in mice and rats administered ethanol.

Several studies examined the genotoxicity of ethanol and alcoholic beverages in human blood lymphocytes *in vitro*. In one study, chromosomal aberrations were induced in human lymphocytes treated *in vitro* with ethanol without exogenous metabolic transformation, but several similar studies were negative. Lymphocyte exposure to different types of alcoholic beverages did not produce chromosomal aberrations.

An increase in SCE was observed in human lymphocytes treated with ethanol or alcohol-free extracts of several alcoholic beverages. One study with ethanol showed a dose-related increase in SCE without exogenous metabolic activation, but another study found an SCE increase only after the addition of alcohol dehydrogenase. In a study of alcohol-free beverage extracts, the frequency of SCE was increased in the absence of an exogenous metabolic system.

5.2 Genotoxicity Studies Published after IARC (1988)

This section reviews only studies in human and other mammalian systems and *Drosophila*. An increase in the frequency of structural chromosomal aberrations was observed in mitogen-stimulated peripheral blood lymphocytes of abstinent alcoholics (Gattas and Saldanha, 1997). Abstinent alcoholics were abstinent from one month to 32 years (n = 55) while controls (n = 55) were selected at random and not screened for alcohol intake. Cytogenetic analyses showed that ex-chronic alcoholics had a threefold higher frequency of cells with structural chromosomal aberrations in peripheral lymphocytes than did controls.

An *in vivo* human study reported no relationship between reported alcohol intake and *hprt* mutant frequency in human T cells (Cole and Green, 1995). Blood samples were taken from 153 normal humans classified into four groups based on alcohol intake. Each donor had completed a questionnaire concerning alcohol consumption. Samples analyzed for *hprt* mutant frequency showed no significant difference in mutant frequency between groups, and there was no correlation between mutant frequency and alcohol consumption.

A study suggested that moderate wine consumption protects against hydrogen peroxide-induced DNA damage (Fenech et al., 1997). Blood samples were taken from four male volunteers just prior to wine consumption and at 1, 3, 8, and 24 hours after consumption of 300 mL of red or white wine. Volunteers were put on a plant polyphenol-free diet 48 hours prior to wine consumption to test the hypothesis that polyphenols in wine have a protective effect. Lymphocytes were exposed to hydrogen peroxide and the frequency of micronucleated cells was determined. Although an apparent protective effect was seen for both red and white wine, only with white wine consumption was there a statistically significant ($p = 0.0068$) inhibition (> 70%) of hydrogen peroxide-induced micronucleated cells observed one hour after consumption. In contrast, there was no effect among samples taken before the polyphenol-free diet, immediately before wine consumption, and 8 or 24 hours after wine consumption. The polyphenol effect is unclear because the white wine had a much lower level of total polyphenols than the red wine.

SCE frequencies were slightly higher in mouse (NIH male) bone marrow cells, 24 hours after i.p. inoculation with ethanol, tequila, or brandy (Piña-Calva and Madrigal-Bujaidar, 1993). Groups were inoculated with four doses of each liquid with the highest dose corresponding to 0.25-0.50% of a previously determined LD_{50}. All beverages at all doses, except ethanol at the lowest dose, produced significant ($p = 0.01$) increases in SCE frequencies compared to distilled water controls. With respect to cellular proliferation kinetics, no change was seen in the average generation time (AGT) for the tested substances.

A study investigated alterations in the synaptonemal complex (SC) of mouse spermatocytes after exposure of male mice to tequila and brandy (Piña-Calva et al., 1997). Three daily doses (1, 2, or 3 g/kg) of each beverage 20% diluted in distilled water were given by oral intubation for 21 days. Distilled water was the negative control and cyclophosphamide (20 mg/kg) served as a positive control. Tequila (2 and 3 g/kg) and brandy (3 g/kg) induced a significant ($p = 0.05$) increase in SC breaks.

The potential genetic toxicology of commercial beers was investigated using Chinese hamster ovary (CHO) cells and observation of SCE, chromosomal aberrations, and hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutation (Ivett et al., 1992). Concentrated organic residues from aliquots of commercial beers were prepared from resin extracted from a blend of four beers. For the SCE assay, cell cultures were treated with 0.75 μL/mL to 10 μL/mL of the extracts. The aberration assay used 1 μL/mL to 10 μL/mL, and the forward mutation assay used 2.5 μL/mL to 20 μL/mL. The SCE assay showed a significant increase in three of five samples without metabolic activation, but no increase after the addition of S9. The chromosome aberration and forward mutation assays were negative with or without metabolic activation of the extracts.

Several wines and a brandy were screened for potential genotoxicity with the Drosophila wing Somatic Mutation and Recombination Test (SMART) (Graf et al., 1994). *Drosophila melanogaster* larvae were fed three concentrations of each beverage for two durations and wing spots on the progeny of certain crosses were examined. Ethanol and water were separate controls. One of the five red wines showed significant genotoxic activity that was apparently unrelated to ethanol content because ethanol alone did not have a genotoxic effect.

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, and Metabolism in Humans and Experimental Animals

6.1.1 Absorption

Ethanol is absorbed from the gastrointestinal tract by simple diffusion (Wallgren and Barry, 1970; cited by IARC, 1988). Absorption from the stomach and upper intestine occurs within the first hour after ingestion (Halsted et al., 1973; cited by IARC, 1988). The absorption rate is decreased by food in the intestine and by delayed gastric emptying, as shown in studies of several animal species (Wallgren and Barry, 1970; cited by IARC, 1988).

A physiologically based pharmacokinetic model for ethanol absorption after inhalation by mice, rats, and humans was developed and validated with experimental data (Pastino et al., 1997). The model accurately predicted the blood ethanol concentrations in rats and mice exposed to 50, 200, and 600 ppm for up to six hours and in humans exposed to various concentrations of ethanol vapor for three hours.

6.1.2 Distribution

Animal studies show that, after diffusion into blood, ethanol is rapidly taken up into brain tissue (Harger et al., 1937; cited by IARC, 1988), but distribution to resting skeletal muscle is relatively slow (Harger and Hulpieu, 1956; cited by IARC, 1988). The rate of loss of ethanol from blood follows zero-order kinetics after intravenous administration in several species (Newman and Lehman, 1937; cited by IARC, 1988).

6.1.3 Metabolism

Ethanol is initially metabolized by oxidation to acetaldehyde through the alcohol dehydrogenase pathway (Smith et al., 1973; cited by IARC, 1988). Acetaldehyde is further metabolized to acetate by aldehyde dehydrogenase (Agarwal et al., 1981; cited by IARC, 1988). The rate of ethanol metabolism varies among individuals because of differences in genetically determined isoenzymes (Smith et al., 1973; cited by IARC, 1988). It has also been reported that some Orientals have a reduced rate of acetaldehyde metabolism (Ijiri, 1974; cited by IARC, 1988).

Acetaldehyde, the major intermediary metabolite of ethanol, is an animal carcinogen (IARC, 1988). A number of studies report the presence of acetaldehyde in alcohol consumers. Acetaldehyde was detected in the serum of Finnish women after intoxication (Fukunaga et al., 1993; cited by Longnecker, 1995) and as a DNA adduct in alcoholics (Fang and Vaca, 1997).

Chronic ethanol consumption results in an increased rate of ethanol metabolism to acetaldehyde (Nuutinen et al., 1984; cited by IARC, 1988), and enhances the metabolism of many drugs and halogenated hydrocarbons (Zimmerman, 1986; cited by IARC, 1988).

6.2 Modification of Toxicokinetics/Dynamics of Carcinogens

It is well known that acute or chronic consumption of ethanol influences the metabolism of other organic compounds, including drugs and some known carcinogens. The detection of nitrosamines in the urine of volunteers given ethanol and amines indicates nitrosamine metabolism is inhibited by ethanol (Eisenbrand et al., 1981; Spiegelhalder and Preussmann, 1985; both cited by IARC, 1988). When volunteers ingested ethanol immediately prior to inhalation of trichloroethylene, trichloroethylene levels in plasma increased twofold and urinary excretion of a main metabolite (trichloroethanol) decreased (Müller et al., 1975; cited by IARC, 1988). Chronic consumption of ethanol increased the metabolism of many drugs and halogenated hydrocarbons to reactive intermediates (Zimmerman, 1986; cited by IARC, 1988) and caused otherwise nontoxic doses of chemicals (e.g. acetaminophen) to become toxic (Seeff et al., 1986; cited by IARC, 1988).

Reduced clearance of the nitrosamine NDMA with coexposure to ethanol was demonstrated for mice (Anderson et al., 1994; cited by Anderson et al., 1995) and patas monkeys (Anderson et al., 1992; cited by Anderson et al., 1995). Dose-dependent effects were observed for several toxicokinetic parameters, including maximum blood concentration, mean residence time, clearance, and area-under-blood-concentration vs. time curve (AUC) for the NDMA.

Hepatic pentobarbital hydroxylase activity in nonalcoholic volunteers doubled after 12 days of ethanol ingestion as 42% of total calories, suggesting an induction of cytochrome P450 (Rubin and Lieber, 1968; cited by IARC, 1988). Likewise, an increase in the smooth endoplasmic reticulum of hepatic cells was observed in volunteers given ethanol as up to 46% of total calories for 16-18 days (Lane and Lieber, 1966; cited by IARC, 1988). Studies with alcoholics also reveal enzyme induction by ethanol, if liver function is uncompromised. Increased levels of hepatic cytochrome P450 were detected in alcoholics with normal liver histology, but not in alcoholics with hepatitis or cirrhosis (Pelkonen and Sotaniemi, 1982; cited by IARC, 1988). Ethanol induced P450 enzymes in various animal tissues, including the liver, lung, intestines, and esophagus (Farinati et al., 1989; Lieber et al., 1987; both cited by Garro and Lieber, 1990).

The expression of a rat liver cytochrome P450 enzyme was reduced by chronic administration of alcohol (van den Wiel et al., 1993; cited by Longnecker, 1995). One study showed inductive and inhibitory effects of ethanol on hepatic mixed function oxidases in hamsters (Ioannides and Steele, 1986; cited by Garro and Lieber, 1990). Ethanol was also shown to be a competitive inhibitor of *N*-nitrosodimethylamine (DMN) demethylase activity in mice (Anderson et al., 1986; cited by Garro and Lieber, 1990). Reduced clearance of NDMA in experimental animals is consistent with competitive inhibition of P450 isoforms by ethanol (Anderson et al., 1995).

6.3 Formation of DNA-Reactive Molecules and DNA Adducts

In addition to acetaldehyde, chronic ethanol exposure can result in the formation of other DNA-reactive molecules, including oxygen radicals and lipid peroxidation products (Brooks, 1997; Garro and Lieber, 1990). Reactive oxygen intermediates, such as the hydroxyl radical, were detected in microsome preparations from experimental animals chronically administered ethanol. Lipid peroxidation products, produced from the reaction of oxygen intermediates and cellular lipids, were also identified in the livers of experimental animals after chronic exposure to ethanol. These molecules can produce DNA strand breaks, oxidative base damage, and form adducts with miscoding potential. Although DNA repair mechanisms are operative in most cells, chronic ethanol exposure places an additional burden on cells damaged during normal metabolism.

A recent study reported detection of DNA adducts of acetaldehyde in peripheral white blood cells of alcohol abusers (Fang and Vaca, 1997). Adduct levels in granulocyte and lymphocyte DNA (measured by ^{32}P-postlabeling using reversed-phase HPLC with on-line detection of radioactivity) were seven and 13-fold higher in alcoholic patients than in controls (p

< 0.001). In alcoholic patients, the average adduct level in granulocyte DNA was 60% higher than the level in lymphocyte DNA. Adduct levels in alcoholic patients indicated a large inter-individual variation.

NDMA-DNA adducts were increased in several tissues of patas monkeys given ethanol just prior to treatment with NDMA (Anderson et al., 1995). The adducts were greatly increased in tissues that are targeted in some human cancers, including the esophagus, ovary, and colon mucosa. In another study, the *in vivo* formation of rat mammary DMBA-DNA adducts was not influenced by chronic ethanol intake at 20% of calories before DMBA administration (Singletary et al., 1991; cited by Singletary, 1997).

The formation of O^6-methyldeoxyguanosine (O^6-MEdG) by the carcinogen *N*-nitrosomethylbenzylamine (NMBzA) was influenced by co-exposure of rats to ethanol (Yamada et al., 1992). Male Fischer rats were given a single intragastric dose of NMBzA in tap water containing 0-20% ethanol or in various alcoholic beverages adjusted to 4% alcohol. O^6-MEdG was increased in the esophagus, lung, and nasal mucosa of rats coadministered ethanol and NMBzA. Esophageal O^6-MEdG was increased in rats coexposed to NMBzA and various alcoholic beverages (pear brandy, sake, farm-made calvados, gin, Scotch whisky, white wine, Pilsner beer). Commercially distilled calvados and red burgundy wine produced significant increases in esophageal O^6-MEdG, indicating effects of ingredients other than ethanol in some alcoholic beverages.

6.4 Cell Proliferation

The proliferation of cells from which mammary adenocarcinomas develop in rats was increased by ethanol intake as 20-30% of calories (Singletary and McNary, 1994). Another recent study investigated the effect of ethanol on the growth of human breast cancer cells *in vitro* (Singletary and Yan, 1996; cited by Singletary, 1997). Ethanol at concentrations between 10-100 mM selectively stimulated the proliferation of estrogen receptor positive (ER+), but not estrogen receptor-negative (ER-) cells.

Increased cell proliferation was observed in the tongue, epiglottis, and forestomach of Wistar rats orally administered acetaldehyde (Homann et al., 1997). This proliferation was indicated by an enlarged basal layer of squamous epithelia in these tissues.

A review of alcohol-associated gastrointestinal cell proliferation in rats and humans concluded that chronic alcohol consumption produces mucosal hyperregeneration in certain sites (Simanowski et al., 1995). In rats chronically fed ethanol, cell proliferation was seen in the esophagus and in the rectum, but not in the colon. Esophageal cell proliferation depended on salivary gland function. In humans, there was an increased proliferative index in the rectal crypt. Ethanol produced cell proliferation in the esophageal epithelium of rats (Haentjens et al., 1987; cited by Garro and Lieber, 1990).

6.5 Cancer Susceptibility from Genetic Polymorphisms

A study strongly suggests that polymorphisms that increase acetaldehyde levels lead to an increased cancer risk (Harty et al., 1997). The risk of oral cancer associated with alcohol consumption was significantly increased in persons with a fast-metabolizing form of alcohol dehydrogenase. This enzyme converts ethanol to acetaldehyde. The immediate contact of acetaldehyde with oral tissues may initiate carcinogenesis.

Other studies also provide evidence of a genetic predisposition to acetaldehyde exposure and further implicate acetaldehyde in neoplasms associated with alcohol (Yokoyama et al., 1996a, 1996b; Yamamoto et al., 1993; all cited by Yokoyama et al., 1996c). The enzyme that metabolizes acetaldehyde, aldehyde dehydrogenase-2, was found to be inactive in a significant proportion of Japanese alcoholics who developed cancer of the upper aerodigestive tract.

Genetic polymorphisms (*Rsa*I and *Dra*I of *CYP2E1* and *Msp*I of *CYP1A1*) were compared among groups of Caucasian alcoholics and a control group (Lucas et al., 1996). Alcoholic groups were distinguished based on presentation of clinical symptoms from ethanol-related diseases, and groups were defined for esophageal cancer and upper aerodigestive tract cancer. The only significant difference was an increased frequency of the *Dra*I polymorphism in alcoholics, with or without ethanol-related diseases, compared with controls. In addition, among patients with the two alcohol-related cancers, the rare *Dra*I-C allele was three times less frequent in patients under age 45 than in older patients.

6.6 Suppression of DNA Repair

In rats, chronic and acute alcohol consumption increased the persistence of dimethylnitrosamine-induced hepatic O^6-methylguanine DNA adducts and acetaldehyde inhibited O^6-methylguanine transferase activity in rats and humans (Garro et al., 1986; Mufti et al., 1988; Espina et al., 1988; all cited by Garro and Lieber, 1990). This enzyme was also inhibited in neutered adult male rats by a single i.p. injection of 30% ethanol and a dose-response relationship was observed (Wilson et al., 1994).

6.7 Alcohol Metabolism by Microorganisms in the Upper Respiratory Tract

In humans, bacteria in the upper respiratory tract metabolize alcohol to acetaldehyde and can generate significant amounts of acetaldehyde that can persist in saliva for an extended period (Homann et al., 1997a; cited by Homann et al., 1997b). Acetaldehyde is considered to be a carcinogen in experimental animals (IARC, 1985). The direct contact of alcohol with tissues in the upper intestinal tract and subsequent conversion by microorganisms to acetaldehyde may contribute to the greater incidence of cancers in these anatomical regions among heavy consumers of alcoholic beverages (Homann et al., 1997b).

6.8 Other Carcinogens in Alcoholic Beverages

Some chemical compounds detected in alcoholic beverages are known or suspected animal or human carcinogens (Table 1-1). Urethan and nitrosamines are examples of compounds identified in all types of alcoholic beverages.

6.9 Dietary Factors

Cancer risk among malnourished alcoholics may be increased by their low intake of fruits and vegetables (Garro et al., 1990; cited by Longnecker, 1995). A lower consumption of carbohydrates among drinkers is the most common dietary difference between drinkers and nondrinkers (Colditz et al., 1991; cited by Longnecker, 1995), but this difference is unlikely to affect cancer risk. The levels of vitamin A in the liver were reduced by ethanol through increased mobilization of vitamin A from the liver to other organs and enhanced degradation of vitamin A by ethanol-induced P450 enzymes (Sato and Lieber, 1981, 1982; cited by Garro and Lieber, 1990). Vitamin A was associated with reduced cancer risk in epidemiological investigations (Ziegler, 1989; cited by Garro and Lieber, 1990). Human data indicate that folate may influence neoplastic changes in association with alcohol, consistent with alcohol interference with absorption and utilization of folate. Men who reported high alcohol consumption and low folate intake had a high risk of rectal cancer (Freudenheim et al., 1991). Another study (Giovannucci et al., 1995) found an increased risk of total colon cancer in association with high alcohol but low folate intake.

Plasma β-carotene levels after recent alcohol intake were affected by liver damage (Ahmed et al., 1994). In cases without signs of liver damage, levels were increased following heavy alcohol consumption, while patients with alcoholic cirrhosis showed a decline in plasma ß-carotene levels after heavy alcohol intake. Another study (Albanes et al., 1996) suggests a possible interaction of alcohol and ß-carotene in the development of lung cancer.

6.10 Hormones

An epidemiology study of premenopausal women found a positive association between alcohol consumption and the estrogen precursor, androstenedione (Dorgan et al., 1994). Another study of premenopausal women (Reichman et al., 1993) reported that alcohol intake was associated with significant increases in plasma and/or urinary levels of several estrogenic hormones, including dehydroepiandrosterone sulfate, estrone, estradiol, and estriol. In a study of post-menopausal women (Hankinson et al., 1995), alcohol consumption was positively associated with estrone sulfate plasma levels, but not with estrone or estradiol.

7.0 MECHANISMS OF CARCINOGENESIS

At least two mechanisms may contribute to the carcinogenicity of alcoholic beverages. One of these is the carcinogenic activity of acetaldehyde, the initial metabolite of ethanol. A second possible mechanism is alteration of the metabolism of known environmental carcinogens such as nitrosamines.

While animal studies do not show that ethanol is a complete carcinogen, IARC (1985) concluded that there is sufficient evidence for the carcinogenicity of acetaldehyde in experimental animals. DNA adducts of acetaldehyde have been detected in lymphocytes of heavy drinkers. Acetaldehyde formation may be facilitated by microorganisms in the upper digestive tract, and a genetic predisposition to rapid acetaldehyde formation may also contribute to the carcinogenicity of alcoholic beverages (section 6).

Studies in humans and animals suggest that ethanol can promote the carcinogenic activity of known carcinogens. The metabolism and clearance of nitrosamines and trichloroethylene was reduced by prior or coexposure to ethanol (section 6). Animals exposed to known carcinogens had a higher cancer incidence with pre- or co-exposure to ethanol (section 4).

Two other possible mechanisms by which alcohol contributes to cancer are interference with folate metabolism and changes in hormone levels (section 6). Men who reported high alcohol consumption and low folate intake had a higher risk of rectal cancer (Freudenheim et al., 1991) and total colon cancer (Giovannucci et al., 1995). These results may reflect the fact that alcohol is an antagonist of methyl-group metabolism and can consequently affect DNA methylation (Giovannucci et al., 1995). An imbalance in DNA methylation is consistently observed in colonic neoplasia (Hoffman, 1984). Alterations of hormone levels by alcohol may also mediate carcinogenesis since endogenous hormones are believed to play a role in the development of breast cancer (Harris et al., 1992). However, mechanisms are speculative and results of alcohol effects on plasma hormones in premenopausal women are inconsistent (Reichman et al., 1993; Dorgan et al., 1994).

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APPENDIX A

DESCRIPTION OF ONLINE LITERATURE SEARCHES FOR ALCOHOLIC BEVERAGE CONSUMPTION

DESCRIPTION OF ONLINE LITERATURE SEARCHES FOR ALCOHOLIC BEVERAGE CONSUMPTION

The search statement used in the biomedical databases MEDLINE, CANCERLIT, and TOXLINE, combined the terms alcoholic beverages OR beer OR wine OR spirits (allowing for both singular and plural forms) with "neoplasms + all/CT", which represents 658 Medical Subject Heading (MESH) terms for neoplasms. A similar search was done in EMBASE. These searches were done in October 1997. Duplicates were removed, and the 958 records were reduced to 777 by limiting to the period 1987-1997.

Current Contents searches in the 1200 Life Sciences journals edition had been done weekly for current awareness since April 1997, when a similar search was done only in TOXLINE with retrievals limited to reviews.

Searches for genetic toxicity information were done in the databases EMIC and EMICBACK.

Production and consumption information was sought in the commercial databases PROMT and the Chemical Economics Handbook. Internet searches led us to statistics from the Beer Institute, the Wine Institute, and the Statistical Abstract of the United States, and to an order form for the recent Report to Congress by the National Institute for Alcoholism and Alcohol Abuse.

APPENDIX B

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK TO HUMANS: ALCOHOL DRINKING (VOLUME 44), 1988

5. EPIDEMIOLOGICAL STUDIES OF CANCER IN HUMANS

As early as 1910, it was observed in Paris, France, that about 80% of patients with cancer of the oesophagus and cardiac region of the stomach were alcoholics, who drank mainly absinthe (Lamy, 1910). In the first half of this century, it was also noted from mortality statistics in various countries that high risks for cancers of the oral cavity, pharynx, oesophagus and larynx occurred among persons employed in the production and distribution of alcoholic beverages (Young & Russell, 1926; Clemmesen, 1941; Kennaway & Kennaway, 1947; Versluys, 1949). Later studies showed that cancers at these sites occur at lower rates of incidence (and mortality) in religious groups that proscribe alcohol intake, such as Seventh-day Adventists (Wynder *et al.*, 1959; Lemon *et al.*, 1964; Phillips *et al.*, 1980), compared with corresponding national populations. Although many aspects of the life style of such populations are particular, differences in drinking (and smoking) habits may contribute to the differences in disease rates. Subsequent to these historical observations and studies of religious groups, analytical studies of the cohort and case-control type have been carried out.

5.1 Measurement of alcohol intake in epidemiological studies

In descriptive studies, discussed below, a very crude level of alcohol intake is typically inferred for a group of individuals, on the basis of characteristics such as treatment for alcoholism. Frequently, even measurements of average alcohol intake in these groups and in the groups with which they are compared are not available.

In case-control and cohort studies involving individual subjects, measurements of alcohol intake are usually obtained by structured interview or questionnaire. The questions asked vary widely among studies, providing markedly different levels of detail about alcohol intake (Room, 1979). In some studies, a single question was asked that provided only a few categories of alcohol consumption. In many studies, separate questions were asked regarding the average frequency (usually in terms of standard units) of drinking beer, wine, spirits and other specific beverages. This information allows a calculation of usual total ethanol intake as well as an estimation of that from the specific beverages. In some studies, further information was collected about alcohol consumption at different ages. In general, details about intraindividual variations, such as 'binge drinking', have not been incorporated in the studies reviewed.

The validity of self-reported alcohol consumption has been reviewed by Midanik (1982). In some populations (Pernanen, 1974), but not necessarily all, self reporting of alcohol intake results in a lower total than that for alcohol sales. However, even if a population as a whole tends to underestimate intake, this may not necessarily be true of participants in epidemiological studies, such as those who volunteer to enrol in a cohort study. Moreover, there is some evidence that underestimation tends to be proportional to consumption, so that the broad ordering of respondents is maintained (Boland & Roizen, 1973).

The reproducibility and validity of the measurements of alcohol consumption used in epidemiological investigations have been examined in several recent studies. Rohan and Potter (1984) interviewed 37 men and 33 women in Australia regarding food and beverage intake twice at a three-year interval; mean intakes were reported almost identically on the two questionnaires, and the correlation between the original report and recalled intake was 0.87 for men and 0.79 for women. In a comparison of intake measured by diet record and a dietary history interview four years later among 79 Dutch men and women, mean alcohol consumption was found to be identical using the two methods, and the correlation among individual subjects was 0.82 (van Leeuwen *et al.*, 1983).

Riboli *et al.* (1986) compared wine intake as assessed by an interviewer-administered questionnaire among 29 Italian adults with consumption reported in a one-week dietary record. The estimate from the questionnaire was about 40% higher than that determined from the diary, and the correlation between the methods was 0.57. In a validation study of a self-administered dietary questionnaire conducted among 173 participants in a large US cohort of women, Willett *et al.* (1987) compared alcohol intake computed from two administrations of a questionnaire at a one-year interval with intake assessed by four one-week diet records collected during the interviewing year. Mean alcohol intake by this group of women was nearly identical whether assessed by either of the two questionnaires or the dietary record: the correlation between the two questionnaires was 0.90, that between the first questionnaire and the diet record, 0.86, and that between the second questionnaire and diet record, 0.90. Furthermore, significant correlations were observed between the questionnaire measure of alcohol intake and plasma high-density lipoprotein-cholesterol levels (which is known to be sensitive to alcohol ingestion), providing qualitative evidence of a physiological response to alcohol intake. It thus appears that alcohol intake can be measured in a reproducible and valid manner by the relatively simple questionnaires employed in many epidemiological studies. Additional characterization of drinking habits, including use of alcohol at different ages and shorter-term patterns of individual variation, may provide useful information and improve the classification of subjects according to long-term alcohol use.

In case-control studies, errors in recall of alcohol intake that are different between cases and controls could distort the relation with cancer risk; it is possible that the occurrence of a grave illness could affect recall. In several studies of dietary recall, it has been noted that current dietary intake has a major influence on the reporting of earlier diet (Jensen *et al.*, 1984). Since alcohol intake may be altered by serious illness or by its treatment, it is possible that studies of prevalent cases of cancer are less reliable than studies of newly diagnosed cases, even if alcohol does not influence prognosis.

5.2 Descriptive studies

Descriptive studies (also referred to as ecological or correlation studies) of the relationship between alcohol consumption and cancer risk entail analysis of the co-variation of population-based measures of those two variables. Variations (known or inferred) in alcohol consumption by time, geographic location and category of person are examined in relation to variations in cancer incidence or mortality rates. Since alcohol consumption tends to be associated with other forms of behaviour that might also influence the risk of developing cancer (especially cigarette smoking and aspects of diet), and for which equivalent measures of exposure are frequently not available, it is not possible in descriptive studies to infer a causal relationship between alcohol consumption and cancer risk. In addition, in descriptive studies, average values of alcohol consumption are attributed to population groups as a whole; depending on the actual distribution of exposures within the population, this can result in considerable misclassification of exposure and consequent errors in estimation of effects.

(*a*) *Geographical and temporal studies*

Geographical and temporal variations in alcohol consumption are usually estimated from systematic records (governmental or commercial) of production and sales, or from changes in the rates of other acknowledged diseases of 'alcohol abuse' (especially alcoholic liver cirrhosis). In some cross-sectional, regional, ecological studies, alcohol consumption in different population subgroups has been estimated by direct survey (e.g., Hinds *et al.*, 1980).

Intrapopulation studies, in which identifiable groups of people with known differences in alcohol consumption (e.g., abstainers, religious groups, ethnic groups) or with known or presumed changes in drinking habits (e.g., migrants) are studied, are also a useful source of descriptive epidemiological data. Again, however, measures of confounding variables are often not available, or, if available, may be difficult to 'control for' in data analysis at the population level.

Descriptive studies have been used most frequently to study alcohol consumption in relation to specific cancers of the upper alimentary tract and larynx. Oesophageal cancers, in particular, have been studied in this way in both developed and developing countries. Many geographic correlation studies have been carried out to examine mortality from alimentary tract cancer in relation to mortality from liver cirrhosis and alcoholism within the departments of France (Lasserre *et al.*, 1967). These studies have consistently shown a strong correlation of oesophageal cancer with the index of alcohol consumption; less strong correlations have been seen for cancers of the mouth, pharynx and stomach. Geographic studies have also been carried out in eastern and southern Africa to examine the substantial local variations in oesophageal cancer mortality in relation to alcohol consumption and to brewing practices (Day *et al.*, 1982). Several international studies have demonstrated a positive correlation between national consumption of beer per head and mortality from cancer of the rectum (Breslow & Enstrom, 1974; Potter *et al.*, 1982).

Time trends in alcohol consumption per head and mortality from selected cancers have been analysed in some countries, predominantly in relation to cancers of the upper alimentary tract and larynx (Tuyns *et al.*, 1977; McMichael, 1979). Positive correlations have been reported consistently for some specific sites. In studies in which simultaneous time trends in several countries have been examined, a role has been suggested for alcohol consumption in the etiology of, for example, cancers of the large bowel (McMichael *et al.*, 1979).

Variations in the male:female ratio of cancer rates in relation to variations in the male:female ratio of mortality from alcoholic liver cirrhosis, or of alcohol consumption as determined by surveys of population samples, have also suggested a role for alcohol consumption in the etiology of cancers of the upper alimentary tract, the larynx, the liver, and, less clearly, the stomach and large bowel (Flamant *et al.*, 1964; Enstrom, 1977; Keller, 1977).

In very few descriptive studies has deliberate attention been paid to the relationship between alcohol consumption and cancers at other possibly relevant sites, such as the breast, pancreas and lung.

(*b*) *Studies of cancer rates in cultural subgroups*

The Mormons (Church of Jesus Christ of Latter-day Saints) expect abstention from alcohol and tobacco by active members; while the Seventh-day Adventists proscribe tobacco smoking, alcohol drinking and meat eating.

Wynder *et al.* (1959) compared the relative frequencies of various cancers in Seventh-day Adventists and in nonmembers recorded in eight US hospitals (83% in California), where Seventh-day Adventists represented approximately 10% of all hospital admissions. There were fewer cancers than expected of the lung (not adenocarcinoma), urinary bladder, uterine cervix, mouth, larynx and oesophagus in the Seventh-day Adventists.

Lemon *et al.* (1964) compared the age- and sex-standardized rates for causes of death of Californian Seventh-day Adventists with those of other Californians in a five-year follow-up of 47 866 members of the Church. A total of 3481 deaths (64.9% of expected for men and 74.1% for women) were reported, and death certificates were obtained for 3451 of them; cancer mortality was 70.6% of the expected value for men and 80.1% for women. The major deficits were in buccal and pharyngeal cancer (3 observed, 16 expected) and lung cancer (19 observed, 50 expected).

Phillips *et al.* (1980) compared cancer mortality among Seventh-day Adventists in California with that of a sample of other Californians who were similar with regard to various demographic and socioeconomic factors. The two cohorts comprised 22 940 Seventh-day Adventists and 112 725 nonmembers, who were followed for 17 (1960-76) and 13 (1960-72) years, respectively, and who had completed the same baseline questionnaire in 1960. Deaths were ascertained by annual follow-up of each study member and by record linkage with the California State death certificate file. Age- and sex-adjusted mortality ratios (Seventh-day Adventists:other Californians and Seventh-day Adventists:US white population for 1960-75) were given for all cancers, for stomach, colorectal, lung, breast and prostatic cancer, and for leukaemias and lymphomas. Significant deficits were detected for all cancers combined, for colorectal cancer, for lung cancer and for other smoking-related cancers.

Jensen (1983) studied 1589 male Copenhagen Temperance Society members in Denmark, 781 of whom were Seventh-day Adventists. Expected numbers of cancer cases were obtained by multiplying sex-, age- and calendar-time-specific incidence rates for the general Copenhagen population by the sex-, age- and time-specific person-years of observation in the several groups. For cancers at all sites, a reduced risk was observed among Seventh-day Adventists (relative risk [RR], 0.7; $p < 0.01$), in contrast to that of members of other temperance societies (RR, 1.1). The author attributed the overall reduction in cancer risk to the deficits of alcohol- and tobacco-related cancers among the Seventh-day Adventists. The risk of cancer of the colon, including cancer of the rectosigmoid junction, was also reduced, whereas the risk for rectal cancer was not significantly different from that of the general population.

A comparison of the cancer incidence rates in Mormons and non-Mormons in Utah, USA, during 1966-70, was carried out by Lyon *et al.* (1976). The study was based on 10 641 cases of cancer in Utah classified according to membership in the Mormon Church. Some beliefs and practices of the Mormon Church include emphasis on family life and education, strict sexual mores, and abstinence from alcohol, tobacco, tea, coffee and nonmedicinal drugs (Lyon *et al.*, 1980). Significantly reduced standardized incidence ratios (SIR) for Mormons:non-Mormons were found for the following cancers: all, 0.9 for men and 0.8 for women; oesophagus, 0.4 ($p < 0.001$) and 0.1 ($p < 0.01$); larynx, 0.4 ($p < 0.001$) and 0.3 ($p = 0.02$); stomach, 0.8 ($p = 0.04$) for men; colon, 0.7 ($p < 0.001$) for women; lung, 0.5 ($p < 0.001$) for men; uterine cervix, invasive, 0.6, *in situ*, 0.4 ($p < 0.001$); and breast, 0.9 ($p = 0.008$) for women. In contrast, male Mormons had slightly but significantly elevated incidences of cancer of the prostate and of the brain and nervous system. The findings were very similar when the analysis was extended to the period 1967-75, thus including 20 379 cases of cancer (Lyon *et al.*, 1980), approximately 90% of which had been histologically confirmed.

Enstrom (1978) examined cancer mortality among male Mormons in California, USA, during 1968-75. The death rate from cancers at combined smoking-related sites was 58% that of the general Californian population, and that from all other cancers, 68%. Most Mormons smoke and drink alcohol about half as much as the general population, being fairly similar in other respects, such as socioeconomic status and urbanization. Active Mormons abstain almost completely from tobacco and alcohol (Enstrom, 1975). In a subsequent report, Enstrom (1980) was able to use Mormon Church records to subdivide the male Mormon population into those who were active members of the Church and those who were not. The deficit in cancer mortality was greater in active than in all male Mormons. For stomach cancer and colon cancer, the age-standardized mortality ratios (SMRs) did not differ noticeably between active and all male Mormons; however, for rectal and lung cancer, the SMRs were much lower in active Mormons (0.4 and 0.2) than in all male Mormons (0.7 and 0.6). [In these studies of Californian Mormons, it is not made clear how well the numerator deaths, as recorded by the state, correspond to the apparent denominator, as provided by the Mormon Church.]

5.3 Analytical studies

(a) General introduction

The relationship between alcohol intake and cancer at a variety of sites has been assessed in many large cohort studies. With few exceptions, detailed information on type of beverage, amount drunk and on smoking was not available. Tobacco smoking and alcohol drinking are often correlated at the individual level, and tobacco smoke is a cause of cancer at many sites that may also be related to alcohol consumption (IARC, 1986a). However, a major methodological advantage of cohort studies over case-control studies is the lesser probability of selection bias and bias with regard to information on exposure. The most detailed evidence about the relationship between alcohol and cancer at individual sites has come from case-control studies, many of which are described in subsequent sections.

Most of the cohort studies have been of the retrospective (historical) type, comparing cancer incidence or mortality in groups with high alcohol intake (e.g., alcoholics and brewery workers) with that of the general population. The distinction between such cohort studies and descriptive studies is not always clear; several of the investigations of religious groups, described above, could be considered cohort studies but were included with the other studies of these groups for coherence. A few prospective (concurrent) cohort studies in which information on drinking and smoking was available for individual cohort members have been of sufficient size for site-specific risks to be determined.

In a number of cohort studies initiated to study cardiovascular disease, total cancer incidence or mortality has been reported; however, because of the absence of site-specific risk estimates, such studies have not been included.

Since, in some of the cohort studies, the risk of cancer at many different sites was examined, their design is described and commented upon here in order to save unnecessary repetition. Studies in which cancer at only one site was studied are described in the relevant section.

The design of the major retrospective and prospective cohort studies is summarized in Table 45.

(i) *Norwegian Alcoholics Study* (Sundby, 1967)

A total of 1722 men discharged during 1925-39 from the Psychiatric Department of an Oslo hospital with a diagnosis of alcoholism were enrolled in the study and observed until the end of 1962. No information was available on drinking and smoking habits of individual cohort members or of the cohort as a whole, but 408 were considered to be vagrant alcoholics. Evidence of persistent alcoholism was available for about 75% of the vagrants and for 50% of the remaining group. Follow-up was virtually complete, with 1061 deaths. Death certificates were located for 1028 of these, and information on cause of death was available for another 28 persons. The observed numbers of deaths were compared with expected numbers based on causes of deaths for all of Norway (496.9) and for Oslo (629.0).

(ii) *Finnish Alcohol Misusers and Alcoholics Study* (Hakulinen *et al.*, 1974)

Between 1944 and 1959, male 'alcohol misusers' were registered by the Finnish State Alcohol Monopoly on the basis of conviction for drunkenness, sanctions imposed by the municipal social welfare boards, and various breaches against the regulations governing alcohol usage. No information was available on the amount of alcohol consumed by the cohort members, nor on types of beverage or smoking habits. The numbers of incident cases of cancer of the oesophagus, of the liver and of the colon among an estimated 205 000 men born 1881-1932 and alive in 1965-68 were obtained by a manual match between the files of the Finnish Cancer Registry for these years and the files of the Alcohol Misusers Registry. Person-years at risk during the period 1965-68 were estimated from samples, and these formed the basis for computing expected numbers of cases. Lung cancer risk was determined in a similar fashion, but for only one-third of the group in 1968.

A second group of men more than 30 years of age, who in 1967-70 had been listed as chronic alcoholics by the Social Welfare Office of Helsinki, were also studied. The mean annual number of such men was estimated to be 4370. No information was available on type or amount of alcoholic beverages drunk or on tobacco smoking, but the persons in the group of chronic alcoholics were heavy alcohol drinkers, most of whom drank cheap, strong beverages, wines and denatured alcohols. Incident cases of cancer occurring during 1967-70 were identified by record linkage with the Finnish Cancer Registry, and expected numbers were derived on the basis of national incidence rates and computed person-years.

[The Working Group noted that cancer incidence was determined over a brief period (four years) of follow-up. Determination of only a small part of the total experience of each of the underlying source populations of alcohol misusers and chronic alcoholics could introduce bias if the distribution of time since entry into the cohort was limited or skewed and if alcohol-related cancer deaths are distributed unevenly over cohort follow-up time.]

(iii) *UK Alcoholics Study* (Nicholls *et al.*, 1974)

A total of 935 patients who had been discharged from four mental hospitals in or near London, UK, during the years 1953-57, or who had died during the key hospitalization and who had been given a primary or secondary diagnosis implicating abnormal drinking, were followed for 10-15 years. Of the total sample, 70 (7.5%) remained untraced and 233 men (34.4%) and 76 women (29.6%) had died; a total of 112.7 deaths was expected (SMR, 2.7). The SMR for all cancers was 1.7 (37 cases, $p < 0.05$) for men and 1.9 (13 cases, nonsignificant) for women. The study was extended to all of England and Wales 1953-64 by Adelstein and White (1976), who covered a total of 1595 men and 475 women. The SMRs for all causes of deaths were 2.1 for men and 2.8 for women.

Table 45. Main characteristics of cohort studies on the relationship between alcohol and cancers at many sites

Study and reference	Period of enrolment	Population at start (effective population)	Duration of follow-up; no. of deaths; no. of cancers	Completeness of follow-up	Information on		
					Type of beverage	Amount of alcohol	Smoking status
Norwegian Alcoholics (Sundby, 1967)	1925-39	1722 men (1693)	37 years; 1061 deaths; 204 ca deaths	98.3%	-	-	-
Finnish Alcohol Misusers	1944-59	Estimated 205 000 men alive in 1965-68 (born 1881-1932)	Incidence of selected ca sites only; 449 ca cases	-	-	-	-
and							
Alcoholics (Hakulinen *et al.* 1974)	1967-70	Mean annual number of men in the registry, 4370	4 years; 81 incident ca cases	-	-	-	-
UK Alcoholics (Nicholls *et al.*, 1974)	1953-57	678 men, 257 women (865)	10-15 years; 309 deaths; 50 ca deaths	92.5%	-	-	-
Massachusetts Alcoholics (Monson & Lyon, 1975)	1930, 1935 or 1940	1139 men, 243 women	41 years; 894 deaths; 105 ca deaths	66%	-	-	-
England and Wales (Adelstein & White, 1976)	1953-64	1595 men 475 women	17 years; 605 men 189 women	-	-	-	-
Dublin Brewery Workers (Dean *et al.*, 1979)	1954-73	- (men)	20 years; 1628 deaths; total no. of ca deaths not stated	-	-[a]	-[a]	-

Table 45 (contd)

Study and reference	Period of enrolment	Population at start (effective population)	Duration of follow-up; no. of deaths; no. of cancers	Completeness of follow-up	Information on		
					Type of beverage	Amount of alcohol	Smoking status
Japanese Prospective (Hirayama, 1979)	1965	122 261 men, 142 857 women (40+ years)	10 years; 27 993 deaths; 7377 ca deaths	–	+	+	+
Danish Brewery Workers (Jensen, 1979, 1980)	1939–63	14 313 men (6 or more months' employment, 14 227)	30 years; 3550 deaths; 951 ca deaths; 1303 incident ca cases	99.4%	–[a]	–[a]	–
US Veterans Alcoholics (Robinette et al., 1979)	1944–45	4401 men	29 years; 1438 deaths; 166 ca deaths	90–98%	–	–	–
Hawaiian Japanese (Blackwelder et al., 1980; Pollack et al., 1984)	1965–68	8006 men (7846)	Av. 14 years; 426 ca deaths (only 5 sites considered)	98%	+	+	+
Kaiser-Permanente (Klatsky et al., 1981)	1964–68	87 926 (8060 men and women)	10 years; 745 deaths; 215 ca deaths	82–92%	–	+	+
Canadian Alcoholics (Schmidt & Popham, 1981)	1951–70	9889 men (9543)	21 years; 1823 deaths; 240 ca deaths	96.5%	–	–[a]	–[a]
Japanese Doctors (Kono et al. 1983, 1985, 1986)	1965	6815 (5135 men)	19 years; 1283 deaths;	94%	–	+	+
Framingham (Gordon & Kannel, 1984)	1950–54	5209 (2106 men, 2641 women)	22 years 1167 deaths; 257 ca deaths (only specific sites)	91%	+	+	+

[a]Estimates of type and/or consumption given for the group

(iv) *Massachusetts Alcoholics Study* (Monson & Lyon, 1975)

The study comprised 1382 persons (1139 men and 243 women) admitted to mental hospitals in 1930, 1935 or 1940 with a diagnosis indicative of chronic alcoholism. No information was provided on the amount or type of alcohol consumed by individuals or by the cohort as a whole, or on smoking habits. Death certificates were traced up to 1 January 1971 for 909 members of the cohort (66%), while the vital status of the remainder was unknown. Because of the high percentage of persons lost to follow-up, absolute death rates could not be calculated; instead, the proportional distribution of deaths by cause in the cohort was compared with that of the USA, taking into account age, sex and calendar time. The analysis was restricted to 894 deaths among whites. [The Working Group noted that the high percentage of loss to follow-up seriously limits the usefulness of these data.]

(v) *Dublin Brewery Workers Study* (Dean *et al.*, 1979)

A list of 1628 deaths during the period 1954-73 was provided by a large brewery in Dublin, Ireland. On the basis of death certificates for all but two of these men and of statistics for the population of employees and pensioners in 1957, 1960, 1967 and 1970, RRs for specific causes of death were estimated employing both national and regional rates. The expected number of deaths was 1675.8 (regional rates). It was estimated from previous research that ethanol intake among the brewery workers was 58 g per day, compared with 16-33 g per day for other groups of the Irish population. Beer (stout) was consumed on the premises. No information was available on individual consumption of alcohol or tobacco; smoking was forbidden at the brewery for many years. [The Working Group noted that the cohort at risk was estimated indirectly as 2000-3000 men at any one time during follow-up, and no individual follow-up of cohort members was performed.]

(vi) *Japanese Prospective Study* (Hirayama, 1979)

In 1965, 122 261 men and 142 857 women aged 40 years and over (91-99% of the census population) were interviewed in 29 health centre districts in Japan. The main items studied were diet, smoking, drinking and occupation. A record linkage system with death registrations was established for the annual follow-up. Associations between alcohol and cancer were investigated on the basis of ten-year follow-ups through 1975, when there were 27 993 deaths from all causes (16 515 for men and 11 478 for women) and 7377 from cancer.

(vii) *Danish Brewery Workers Study* (Jensen, 1979, 1980)

A total of 14 313 male members of the Danish Brewery Workers' Union who had been employed for six or more months in a brewery during the period 1939-63 were enrolled in this retrospective cohort study. The brewery workers had the right to consume six bottles (2.1 l) of light pilsener (lager) beer (alcohol content, 3.7 g [~78 g ethanol] per 100 ml) on the premises of the brewery per working day; 1063 members of the cohort worked in a mineral-water factory, with no free ration of beer. No information was available on alcohol consumption or smoking habits of individual members of the cohort; but, on the basis of comparisons with alcohol statistics and population surveys, it was estimated that cohort members with employment in a brewery had a four times higher average beer consumption than the general population. Vital status was ascertained for 99.4% of the cohort members.

There were 3550 deaths (SMR, 1.1) in the cohort, and 1303 incident cases of cancer were identified during the period 1943-72 by record linkage with the Danish Cancer Registry. Expected numbers of cancer cases and deaths were computed on the basis of age-, sex-, residence- and time-specific rates. Relationships between use of alcohol and tobacco and cancer of the pharynx, larynx and oesophagus were further explored in a nested case-control study (Adelhardt *et al.*, 1985).

(viii) *US Veterans Alcoholics Study* (Robinette *et al.*, 1979)

A cohort of 4401 US Army service men hospitalized for chronic alcoholism in 1944-45 was drawn as a sample from records of the US Department of Defense and the Veterans' Administration. Of these, 98% were <40 years of age at the time of hospitalization. They were matched for age with an equal number of enlisted men hospitalized for acute nasopharyngitis during the same period. Deaths in these groups were ascertained through the Veterans' Administration Beneficiary Identification and Records Locator Subsystem, and death certificates were obtained to code for cause of death. Follow-up for death was estimated to be 90-98% complete. No information was available on the drinking habits of individual members of the cohort or on average consumption by the cohort members. It was noted that only 7.5% of the chronic alcoholics had been discharged from military service for medical disability, including alcoholism. The mortality experience of the cohort was compared with that of the matched cohort of nasopharyngitis patients, and the mortality of both cohorts was compared with that of US males for selected causes of death. Overall mortality was approximately 80% higher in the alcoholics group than in the nasopharyngitis group (SMR, 1.9).

(ix) *Hawaiian Japanese Study* (Blackwelder *et al.*, 1980; Pollack *et al.*, 1984)

A detailed interview questionnaire on diet, alcohol consumption, smoking history, socioeconomic factors and demographic variables was given to a cohort of 8006 Japanese men included in a study of cancer in Hawaiian Japanese during 1965-68. Because only about 2.5% of the subjects had moved from Oahu, Hawaii, after the initial examination, the authors considered that the surveillance system had allowed identification of virtually all newly diagnosed cancer cases in the cohort. Two kinds of information on alcohol consumption were obtained at interview: usual monthly consumption of wine (including Japanese saké and fortified wines), beer and spirits (including whisky, gin and brandy), and actual intake of each during the 24-h period preceding the interview. Information on usual consumption was converted into ounces of each type of beverage consumed per month and total ounces of ethanol consumed per month. Subsequent cancers occurring up to 31 December 1980 (the average follow-up period was 14 years) were identified from many sources, including the Hawaii Tumor Registry. The relation between alcohol consumption and epithelial cancers of the stomach, colon, lung, rectum and prostate was analysed, controlling for age and cigarette smoking.

(x) *Kaiser-Permanente Study* (Klatsky *et al.*, 1981)

Between July 1964 and August 1968, 87 926 persons responded to a self-administered questionnaire on alcohol intake as part of a multiphasic health examination in Oakland or

San Francisco, California, USA. This corresponded to 48% of the Kaiser Foundation Health Plan members in 1968. Of these, 22.6% reported that they had not drunk alcohol during the preceding year; 8% did not respond satisfactorily. Of 2084 persons who reported taking six or more drinks per day, 2015 were matched to equal numbers of persons who reported taking three to five drinks per day, two or fewer drinks per day, or total abstinence. The overall mortality of persons taking six or more drinks a day was twice that of those taking two or fewer drinks a day. Matching was for sex, race, presence or absence of current cigarette smoking, examination date and age. Altogether, 745 deaths occurred during ten years of follow-up among the 8060 persons in this study. Deaths were ascertained only from the California death index, and it was estimated that 82-92% of all deaths had been identified.

(xi) *Canadian Alcoholics Study* (Schmidt & Popham, 1981)

The cohort consisted of 9889 men (79% middle-class; <1% nonwhite) who had been admitted to the main clinical services for alcoholics in Ontario between 1951 and 1970. No information on individual drinking or smoking habits was available, but investigations of samples of the cohort indicated an average daily consumption of 254 ml [~ 200 g] ethanol and that >92% were still drinking ten years after admission. A total of 94% of cohort members were current smokers, who smoked an average of 28 cigarettes per day. Altogether, 1823 deaths occurred before 1972; 960.9 were expected. Vital status could not be determined for 3.5% of cohort members. Cause-specific mortality was compared with that of the Ontario male population. A further comparison was made with US veterans who smoked 21-39 cigarettes per day, in an indirect attempt to control for the effect of tobacco on the risk of alcohol-related cancers. Results were also reported for 1119 women followed up for 14 years, but only a few cancer deaths were observed (Schmidt & de Lint, 1972).

(xii) *Japanese Doctors Study* (Kono *et al.*, 1983, 1985, 1986)

A survey of smoking and drinking habits was carried out in March and April 1965 on 6815 male physicians in western Japan by means of a self-administered questionnaire. Of these, 5477 provided sufficient identifying information for prospective follow-up; 5135 provided sufficient information on drinking and smoking to classify them as nondrinkers (21%), ex-drinkers (10%), occasional drinkers (31%) and drinkers by daily intake. Similarly, quantitative information on cigarette smoking was available. Follow-up over 19 years revealed 1283 deaths, and was estimated to be 94% complete.

(xiii) *Framingham Study* (Gordon & Kannel, 1984)

Mortality from cancers of the lung, colon, stomach and breast in relation to alcohol consumption was studied in a cohort of 5209 men and women in Framingham, MA, USA. Alcohol consumption, recorded during 1950-54, was examined in relation to cancer mortality over 22 years of follow-up and obtained from 2106 men and 2641 women. [The Working Group noted that cancer is considered in only one table, analysed by a multivariate technique, but the levels of alcohol consumption included in the analysis are not specified.]

(*b*) *Cancer of the oral cavity and pharynx*

Since nasopharyngeal cancer is rare in most of the countries in which studies have been carried out, it can be assumed that the pharyngeal cancers referred to are predominantly of the oro- and hypopharynx. It is often difficult to determine whether cancers of the oral cavity or pharynx arise in one or other adjacent part classified as different sites in the International Classification of Diseases (ICD) since 1950. For this reason, and because the incidence of tumours at these sites is relatively low, investigators have grouped tumours of the oral cavity and pharynx together in different ways. This may affect the estimates of risk since the strength of the association with alcohol drinking may vary for adjacent parts of the buccal cavity and pharynx.

The risks for oral cavity and pharyngeal cancer in relation to alcohol consumption are summarized in Tables 46-49; whenever the information has been available, the composition of the tumour group has been given.

(i) *Cohort studies* (descriptions of studies of cancers at many sites are given on pp. 158-164)

Increased mortality from cancer of the oral cavity and pharynx has been observed in people with occupations involving high alcohol consumption (Young & Russell, 1926; Registrar General, 1958; Logan, 1982).

The results of the few available cohort studies are summarized in Table 46. Increased relative risks were found in all, notably in the studies of alcoholics carried out in Norway and Finland (Sundby, 1967; Hakulinen *et al.*, 1974), while the RR was only marginally increased among Danish brewery workers (Jensen, 1980).

Alcoholics in Norway, the USA and Canada had RRs for oral cavity and pharyngeal cancer that were two to five times higher than those of the general populations used for comparison (Sundby, 1967; Monson & Lyon, 1975; Robinette *et al.*, 1979; Schmidt & Popham, 1981). No account could be taken of tobacco smoking, which is known to increase the risk for oral cavity and pharyngeal cancer (IARC, 1986a); however, the RR was still increased when mortality from oral cavity and pharyngeal cancer among Canadian alcoholics was compared with that of US veterans who smoked similar numbers of cigarettes per day (3.3-17.7 according to number of cigarettes smoked per day; Schmidt & Popham, 1981). In the Kaiser-Permanente study (Klatsky *et al.*, 1981), the risk for cancer of the oral cavity, pharynx and oesophagus combined was four times higher among consumers of six or more drinks per day than among nondrinkers roughly matched for smoking habits. The RR was only slightly increased (1.4) among Danish brewery workers with an above-average beer consumption (Jensen, 1980). In the Japanese Doctors study, Kono *et al.* (1986) found an increasing risk for cancer of the upper digestive and respiratory tracts with increasing amount of alcohol taken per day, but the data are presented for all of the oral cavity, pharynx, oesophagus and larynx combined. The association remained after stratifying for tobacco consumption.

(ii) *Prevalence study*

Between March 1964 and September 1966, 346 cases (296 male, 47 female, three of

Table 46. Relative risks for oral cavity and pharyngeal cancer in cohort studies

Study and reference		Number of subjects	Relative risk	95% CI	Comments
Oral cavity					
Norwegian Alcoholics (Sundby, 1967)		13 deaths	5.0	[2.6–8.6]	Comparison with Oslo population
Danish Brewery Workers (Jensen, 1980)		18 cases	1.4	0.9–2.3	
Pharynx					
Norwegian Alcoholics (Sundby, 1967)		9 deaths	4.4	[2.1–8.5]	Comparison with Oslo population
Finnish Alcoholics (Hakulinen *et al.*, 1974)		3 cases	5.7	[1.2–16.5]	
Danish Brewery Workers (Jensen, 1980)		12 cases[b]	1.9	1.0–3.4	
Oral cavity and pharynx[c]					
Norwegian Alcoholics (Sundby, 1967)		22 deaths	4.8	[3.0–7.2]	Comparison with Oslo population
Massachusetts Alcoholics (Monson & Lyon, 1975)		13 deaths	3.3	[1.8–5.6]	
US Veterans Alcoholics (Robinette *et al.*, 1979)		14 deaths	2.2	1.1–4.6	90% CI
Danish Brewery Workers (Jensen, 1980)		46 cases	1.3	0.9–1.7	Includes lip
		11 deaths	0.8	0.4–1.5	
Canadian Alcoholics (Schmidt & Popham, 1981)		24 deaths	4.2	[2.7–6.3]	Comparison with Ontario population
			7.2	[5.0–10.7]	Comparison with US veterans
Kaiser-Permanente (Klatsky *et al.*, 1981)		15 deaths[d]	4.0	1.7–7.9	Comparison of consumers of 6+ drinks/day *versus* 0 drinks/day, adjusted for tobacco use
Japanese Doctors (Kono *et al.*, 1986)	Occasional drinkers	3 deaths[e]	[1.0]	–	Crude RR not changed by adjustment for smoking
	<2 *go*[f]/day	3 deaths[e]	[1.5]	[0.8–2.4]	
	≥2 *go*/day	12 deaths[e]	[8.6]	[6.9–10.6]	

[a] Confidence interval; [ ] when calculated by the Working Group
[b] Excludes nasopharynx
[c] Includes different tumours, depending on study (see text)
[d] Includes oesophagus
[e] Includes oesophagus and larynx
[f] *go* = 27 ml alcohol

unknown sex) of oral and oropharyngeal cancer were diagnosed in Mainpuri District of India (Wahi, 1968). In a study of the prevalence of this cancer in relation to various population characteristics, information was elicited on chewing, smoking and drinking habits and occupation among the oral cancer cases and for a 10% sample of the population. Altogether, 34 997 persons aged 35 years and over were thus interviewed, and period prevalence rates were calculated; those for regular drinkers and nondrinkers were 9.17 and 0.89 per 1000, respectively. The author noted that it was difficult to obtain reliable information about drinking habits in India.

(iii) *Case-control studies*

Cancer of the oral cavity: Data are summarized in Table 47.

In a study of 462 white men with histologically verified squamous-cell carcinoma of the oral cavity and 81 with pharyngeal cancer, Wynder *et al.* (1957a) compared smoking and drinking habits, as well as a number of other risk factors, with those of 207 controls, who did not differ from the cases with regard to age, religion, educational background or hospital status. Information on exposures was obtained by personal interviews carried out in hospitals. The RR increased with increasing number of units (drinks) per day, irrespective of the type of alcoholic beverage. One unit was defined as 8 oz beer [about 9.5 g ethanol], 4 oz wine [about 12 g] or 1 oz whisky [about 9.5 g]. Dose-response relationships remained for both whisky and beer as the predominant drink after adjustment for tobacco smoking. A particularly strong association with alcohol drinking was found for cancers of the floor of the mouth and of the tongue.

In France, Schwartz *et al.* (1962) studied the smoking and drinking habits of 3937 male patients with cancers at various sites and 1807 controls admitted to hospital for traffic and work accidents in Paris and certain other French towns during 1954-58. Controls were matched to patients by age, sex and interviewer. A personal interview elicited information on tobacco smoking, consumption of alcoholic beverages, diet, socioeconomic factors and hereditary factors. In addition, the interviewer sought objective signs of alcoholism. Alcohol intake was measured as the average consumption over the ten years prior to interview. Since patients admitted for accidents are likely to have a higher alcohol consumption than the population giving rise to the cases, alcohol consumption was also compared with that of a second control group consisting of 1196 men with cancers assumed to be unrelated to use of alcohol or tobacco (cancers of the stomach, small intestine, colon, rectum, other digestive system, skin, kidney, prostate, penis, nervous system, endocrine system). No association with alcohol drinking was found for cancer of the lip (49 cases) or for cancer at other sites in the oral cavity after adjustment for tobacco consumption, in comparison with the accident controls. However, alcohol consumption was significantly higher among cases of cancers of the tongue (164 cases; 153 ml [121 g] ethanol/day) and of the oral cavity (144 cases; 138 ml [109 g] ethanol/day), when compared with cancer controls (113 ml [89 g] ethanol/day). [The Working Group noted that RRs could not be calculated from the data presented.]

Vincent and Marchetta (1963) investigated the alcohol and tobacco consumption of 33 men and nine women with cancer of the oral cavity and of 100 male and 50 female controls.

Table 47. Summary of results of case-control studies on oral cavity cancer and alcohol consumption

Place (reference) Site	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
USA, New York (Wynder et al., 1957a) Lip, floor of mouth, gum, buccal mucosa, tongue, palate	Men (462, 207)	Never	1.0	–	Crude RR calculated by the Working Group; incidence study
		<1 unit/day	1.2	0.6–2.8	
		1–2 units/day	1.4	0.6–3.1	
		3–6 units/day	3.1	1.3–7.4	
		>6 units/day	5.2	2.2–12.4	
USA, Buffalo (Vincent & Marchetta, 1963) Tongue[c], floor of mouth, palate, gingiva, buccal mucosa	Men (33, 100)	Nondrinkers	1.0	–	Crude RR calculated by the Working Group
		<2 oz [47 g]/day	1.7	0.5–5.9	
		>2 oz [47 g]/day	9.7	3.0–31.9	
	Women (9, 50)	Nondrinkers	1.0	–	
		<2 oz [47 g]/day	5.1	0.9–28.9	
		>2 oz [47 g]/day	41.0	3.4–495.3	
Sri Lanka (Hirayama, 1966) Lip, floor of mouth, tongue[c], buccal mucosa	Men and women (76, 228)	Nondrinkers	1.0	–	RR adjusted for chewing, calculated by the Working Group
		Drinkers	1.5	0.9–2.8	
Puerto Rico (Martinez, 1969) Lip, floor of mouth, tongue, other mouth	Men (108, 108)	None	1.0	–	Crude RR calculated by the Working Group based on pairs matched for age and smoking
		≤1 unit/day	0.5	0.2–1.5	
		2–4 units/day	1.7	0.7–3.9	
		≥5 units/day	2.8	1.1–7.0	
	Women (30, 30)	None	1.0	–	
		≥ 1 unit/day	0.8	0.2–3.6	
USA, Buffalo (Bross & Coombs, 1976) Mouth, tongue	Women (145, 1973)	Nondrinkers	1.0	–	RR adjusted for age and smoking, calculated by the Working Group
		<30 drinks/month	1.3	0.8–2.2	
		≥30 drinks/month	3.4	1.7–6.6	
USA, Buffalo (Graham et al., 1977) Lip, tongue, floor of mouth, gum, other mouth	Men (584, 1222)	<1 drink/week	1.0	–	Crude RR
		1–6 drinks/week	1.1	0.8–1.5	
		7–13 drinks/week	2.0	1.3–3.0	
		≥14 drinks/week	2.7	1.9–3.7	

Table 47 (contd)

Place (reference) Site	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
USA, Multicenter (Williams & Horm, 1977)					
Lip, tongue	Men (74, 1788)	Nondrinkers	1.0		RR adjusted for age, race and smoking; 95% CI could not be calculated
		≤50 oz-year	1.0		
		≥51 oz-year	1.4	NS	
	Women (20, 3188)	Nondrinkers	1.0		
		≤50 oz-year	0.7		
		≥51 oz-year	9.7	$p < 0.01$	
Gum, mouth	Men (53, 1788)	Nondrinkers	1.0		RR adjusted for age, race and smoking; 95% CI could not be calculated
		≤50 oz-year	2.0	NS	
		≥51 oz-year	3.7	$p < 0.01$	
	Women (25, 3188)	Nondrinkers	1.0		
		≤50 oz-year	1.2	NS	
		≥51 oz-year	1.5	NS	
Canada, British Columbia (Elwood *et al.*, 1984) Tongue, gum, floor of mouth, other	Men and women (133, 133)	<1 oz [24 g]/week	1.0		RR adjusted for smoking and other risk factors; 95% CI could not be calculated
		1-4 oz [24-96 g]/week	1.1		
		5-9 oz [120-216 g]/week	1.4		
		10-20 oz [240-480 g]/week	1.8		
		≥20 oz ≥480 g]/day	4.5		
France, Paris (Brugère *et al.*, 1986) Lip	Men (97, unk.)	0-39 g/day	1.0	-	RR adjusted for smoking; control group from national survey; 95% CI from paper
		40-99 g/day	1.8	0.8-3.9	
		100-159 g/day	4.9	2.1-11.4	
		160+ g/day	10.5	4-27.7	
Tongue, gum, floor of mouth, buccal mucosa	Men (759, unk.)	0-39 g/day	1.0	-	RR adjusted for smoking; control group from national survey; 95% CI from paper
		40-99 g/day	2.7	1.8-4.1	
		100-159 g/day	13.1	8.2-20.8	
		160+ g/day	70.3	42.8-115.4	

[a] g = pure ethanol
[b] Confidence intervals, calculated by the Working Group, when possible, unless otherwise specified; NS, not significant
[c] Anterior two-thirds of the tongue

Controls were selected from the gastrointestinal clinic of the same hospital that gave rise to the cases and were in the same age groups. Crude RRs of 9.7 and 41 (based on three cases, calculated by the Working Group) were seen for men and women who consumed ⩾2 oz [47 g] ethanol per day when compared with nondrinkers.

As part of a study of risk factors for oral cancer in Southeast Asia, Hirayama (1966) inquired about drinking, chewing and smoking habits in Sri Lanka. Seventy-six patients with histologically verified oral cavity cancer (54 men, 22 women) and 228 age- and sex-matched controls were interviewed personally about their exposures. There was an association between alcohol drinking and cancer in the whole group (RR, [3.4]; $p < 0.01$) and among nonchewers (RR, [6.2]; $p < 0.05$). [When adjustment was made for tobacco chewing, a RR of 1.5 (95% confidence interval [CI], 0.9-2.8) was found for alcohol drinkers compared with nondrinkers.]

In Puerto Rico, Martinez (1969) studied 153 cases (115 male, 38 female) of squamous-cell carcinoma of the oral cavity and 488 controls (345 male, 144 female) matched for age and sex, as part of a larger investigation including cancers of the oesophagus and pharynx. The study included all cases diagnosed in hospitals and clinics in Puerto Rico during 1966, and three controls for each case, consisting of one patient from the same hospital or clinic at which the case was diagnosed and two neighbourhood controls; the hospital and neighborhood controls were homogeneous for most variables. Information on drinking, smoking and dietary habits was obtained by personal interview. Possible confounding by tobacco use was eliminated by studying a subset of cases and controls also matched on tobacco consumption. The risk for cancer of the oral cavity in men increased with increasing units of alcohol (18 oz beer [~ 21 g ethanol], 8 oz wine [24 g ethanol], 2 oz spirits [19 g ethanol]) taken per day, after taking account of smoking: 0.5 for <1 unit/day; 1.7 for 2.4 units per day; and 2.8 for ⩾5 units per day. No association was seen for the small group of women.

Two studies were based on interviews of patients admitted to the Roswell Park Memorial Institute in Buffalo, NY, USA. Bross and Coombs (1976) compared the drinking habits of 145 white women with cancer of the mouth and tongue with those of 1973 controls with non-neoplastic diseases. All information was elicited by personal interview prior to the final diagnosis used for determining the case-control status of the persons. [After adjustment for age and smoking, persons who consumed 30 or more drinks of spirits, bottles of beer or glasses of wine per month had a RR for oral cavity and tongue cancer of 3.4 (95% CI, 1.7-6.6) compared with nondrinkers.] The influence of alcohol was seen in particular among women age 40-64 years at diagnosis. Similar RRs were seen for oral cavity and for tongue cancer separately. Graham *et al.* (1977) compared drinking, smoking and dietary habits and dentition status for 584 white men with histologically confirmed cancer of the oral cavity and 1222 white male controls diagnosed at the same hospital between 1958-65. The crude RR increased with increasing number of drinks taken per week to 2.7 ($p < 0.0001$) in those drinking ⩾14 drinks per week. This increase in risk persisted after adjustment for smoking and poor dentition, also identified as risk factors in this study.

The Third National Cancer Survey conducted in the USA in 1967-71 (Cutler *et al.*, 1974) included a patient interview study (Williams & Horm, 1977). A total of 7518 cancer patients were interviewed (57% of those randomly selected for an interview), and the questions included amount and duration of alcohol and tobacco consumption. Quantitative lifetime drinking histories were obtained only for persons who had consumed at least one form of alcohol at least once weekly for at least one year; persons who had never drunk this often were counted as nondrinkers. Drinking and smoking habits of persons with cancers at individual sites known from other studies to be strongly associated with tobacco and alcohol were compared with the habits of persons with cancers at all remaining 'unrelated' sites. These controls consisted of 2102 men and 3464 women. RRs for consumption of wine, beer, spirits and total ethanol were calculated for each related site, adjusted for sex, age and smoking, as compared to other unrelated sites combined. The cut-off point between the two levels of consumption was 51 oz-years, calculated from units/week × number of years of consumption, the unit being glass, can and jigger for the three forms of alcohol used, which were converted to ounces of total ethanol using a standard conversion formula. Lifetime alcohol consumption of 74 men with cancers of the lip and tongue was compared with that of 1788 men with cancers not known to be related to either smoking or drinking. A nonsignificant RR of 1.4 emerged for men with a consumption of ≥51 oz-years ethanol after adjustment for age, race and smoking. Among the 20 women with these cancers, a significantly increased RR of 9.7 was seen for heavy drinkers in comparison with nondrinkers; no elevated risk (RR, 0.7) was seen in those drinking <51 oz-years. Among 53 men with cancer of the gum and mouth, consumers of ≥51 oz-years ethanol had an increased risk (3.7; $p < 0.01$), and the RR increased with increasing lifetime consumption. For 25 women, the RR was not significantly increased (1.2 and 1.5 in those with <51 and with ≥51 oz-years, respectively).

A study of oral cavity, pharyngeal and laryngeal cancers in British Columbia, Canada (Elwood *et al.*, 1984), included 133 cases (83 male, 50 female) of cancer of the oral cavity diagnosed between 1977 and 1980; 133 hospital controls with other cancers were individually matched for age, sex, clinic and time of diagnosis. Patients with diseases presumed by the authors to be unrelated to smoking and alcohol use were included in the control group, which comprised patients with stomach, colorectal and breast cancer. Information on drinking and smoking habits, together with information on social and occupational factors, was obtained by personal interviews. After adjustment for smoking, socioeconomic group, marital status, history of tuberculosis and dental care, a significant increase in trend and risk was observed with increasing amount of alcohol consumed per week. The association with alcohol drinking was stronger than that for smoking.

In France, Brugère *et al.* (1986) reported on systematically recorded information on tobacco use and alcohol consumption for 2540 male cancer patients treated at the Head and Neck Department of the Curie Institute in Paris between 1975 and 1982. Since no control group was available, they compared the alcohol and tobacco consumption of the patients, as recorded on hospital charts, with the consumption of the general population elicited as part of a national survey on health and medical care; for persons in the national survey, the figures were converted to intake in grams of ethanol per day by means of standard measures. A sample of the persons enrolled in the national survey, stratified by age, was used as controls. After adjustment for smoking, the RR for lip cancer among 97 men increased with increasing daily consumption of ethanol, and increasing RRs were also seen among 759 men with cancers of the tongue, gum, floor of mouth and buccal mucosa. [The Working Group noted that information on tobacco and alcohol use was obtained by means of different methods and in different interview situations for cases and controls; the size of the control group is not given.]

Cancer of the pharynx: Six of the studies reviewed above also examined the RR for cancer of the pharynx or epilarynx, when specified, in relation to alcohol intake (Wynder *et al.*, 1957a; Vincent & Marchetta, 1963; Martinez, 1969; Williams & Horm, 1977; Elwood *et al.*, 1984; Brugère *et al.*, 1986). The results of these studies are summarized in Table 48. In all of these investigations, the RR for pharyngeal cancer increased with increasing consumption of alcohol. This increase in risk was also noted in the studies in which the effect of smoking (Martinez, 1969; Williams & Horm, 1977; Brugère *et al.*, 1986), socioeconomic group, marital status, dental care and history of tuberculosis (Elwood *et al.*, 1984) could be taken into account.

A study in Sweden showed that male cases of cancer of the upper hypopharynx (32 patients) and possibly those with cancer of the lower hypopharynx (nine patients) had a higher alcohol intake than 115 controls. No difference was seen for women with regard to cancer of the hypopharynx or cancer of the oral cavity (Wynder *et al.*, 1957b).

Schwartz *et al.* (1962; see description, p. 167) found a higher daily alcohol consumption among 206 cases of hypopharyngeal cancer in France (157 ml/day [~ 124 g ethanol/day]) than among accident controls (126 ml/day [~ 100 g/day]), which was significant after adjustment for tobacco use and after comparison with cancer controls (113 ml/day [~ 89 g/day]). The alcohol consumption of 141 cases of oropharyngeal cancer was significantly higher (144 ml/day [~ 114 g/day]) than that of the cancer controls.

Olsen *et al.* (1985a) studied 32 cases of hypopharyngeal cancer in Denmark (26 male, six female) below the age of 75 years, diagnosed in five treatment centres of the country during the period 1980-82. Controls (1141) were selected at random from the population register and stratified for age, sex and place of residence. Smoking and drinking habits were elicited by self-administered questionnaire. [A nonsignificant RR of 1.8 (95% CI, 0.7-3.3) was calculated for persons who consumed ≥150 g ethanol per week when compared with persons who consumed less, after adjustment for age, sex and tobacco use.]

Tuyns *et al.* (1988) studied 1147 male cases of hypopharyngeal and laryngeal cancer together with 3057 male population controls in France, Italy, Spain and Switzerland. Detailed information on drinking, smoking and dietary habits was obtained by personal interview. After meticulous reclassification of the site of origin of the cancer, there were 281 cases of hypopharyngeal cancer (piriform sinus, postcricoid area, posterior wall, and hypopharynx unspecified) and 118 cases of epilaryngeal cancer at the junction between the pharynx and larynx (epiglottis, aryepiglottic fold, arytenoid and epilarynx unspecified). The RR increased steeply with daily alcohol consumption, taking account of smoking, age and place of residence.

Cancer of the oral cavity and pharynx combined: In two studies, the risk associated with alcohol drinking has been investigated for cancer of the oral cavity and pharynx together. The results of these studies are summarized in Table 49.

Table 48. Summary of results of case-control studies on pharyngeal cancer and alcohol consumption

Place (reference) Site	Subjects (cases, controls)	Total alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
USA, New York (Wynder & Bross, 1957; Wynder <u>et al.</u>, 1957a) Tonsils, pharynx	Men (81, 207)	Never	1.0	–	Crude RR calculated by the Working Group
		<1 unit/day	0.7	0.2–3.6	
		1–2 units/day	1.1	0.2–5.3	
		3–6 units/day	4.4	0.9–21.1	
		>6 units/day	7.7	1.9–31.2	
USA, Buffalo (Vincent & Marchetta, 1963) Piriform sinus, tonsillar fossa and pillar, hypopharynx, posterior third of tongue	Men (33, 100)	Nondrinkers	1.0	–	Crude RR calculated by the Working Group
		<47 g/day	3.8	0.5–28.7	
		>47 g/day	52.5	12.7–217.0	
	Women (7, 50)	Nondrinkers	1.0	–	
		<47 g/day	2.6	0.2–28.5	
		>47 g/day	82.0	14.0–481.2	
Puerto Rico (Martinez, 1969) Naso-, meso- and hypopharynx, pharynx, unspecified	Men (39, 39)	None	1.0	–	RR based on pairs matched for age and tobacco use
		≤1 unit/day	4.1	0.6–26.2	
		2–4 units/day	1.4	0.2–9.8	
		>5 units/day	14.7	2.4–89.7	
USA Multicenter (Williams & Horm, 1977) Pharynx	Men (47, 1788)	Nondrinkers	1.0		RR adjusted for smoking, age and race; 95% CI could not be calculated
		≤50 oz-year	1.9		
		≥51 oz-year	6.2	$p < 0.01$	
	Women (18, 3188)	Nondrinkers	1.0		
		<50 oz-year	1.7		
		≥51 oz-year	17	$p < 0.01$	
Denmark (Olsen <u>et al.</u>, 1985a) Hypopharynx	Men and women (32, 1141)	<150 g/week	1.0	–	RR adjusted for age, sex and smoking by the Working Group
		≥150 g/week	1.8	0.7–3.3	
France, Paris (Brugère <u>et al.</u>, 1986) Oropharynx	Men (634, unk.)	0–39 g/day	1.0	–	RR adjusted for smoking; control group from national survey; 95% CI from paper
		40–99 g/day	2.6	1.6–4.2	
		100–159 g/day	15.2	9.2–25.1	
		160+ g/day	70.3	41.2–120	

Table 48 (contd)

Place (reference) Site	Subjects (cases, controls)	Total alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
Hypopharynx	Men (366, unk.)	0–39 g/day	1.0	–	RR adjusted for smoking; control group from national survey; 95% CI from paper
		40–99 g/day	3.3	1.4–7.9	
		100–159 g/day	28.6	12.5–65.1	
		160+ g/day	143.1	61.9–330.5	
Epilarynx	Men (217, unk.)	0–39 g/day	1.0	–	RR adjusted for smoking; control group from national survey; 95% CI from paper
		40–99 g/day	1.9	0.9–4.8	
		100–159 g/day	18.7	8.1–42.9	
		≥160 g/day	101.4	44–233.9	
Canada, British Columbia (Elwood et al., 1984) Oropharynx and hypopharynx, other	Men and women (87, 87)	<24 g/week	1.0		RR adjusted for smoking and other risk factors; 95% CI could not be calculated
		24–120 g/week	3.7		
		120–210 g/week	6.8		
		210–450 g/week	12.2		
		≥450 g/week	12.1		
France, Italy, Spain, Switzerland (Tuyns et al., 1988)					
Hypopharynx	Men (281, 3057)	0–20 g/day	1.0	–	RR adjusted for smoking, age and area of residence; 95% CI from paper
		21–40 g/day	1.6	0.7–3.4	
		41–80 g/day	3.2	1.6–6.2	
		81–120 g/day	5.6	2.8–11.2	
		≥121+ g/day	12.5	6.3–25.0	
Epilarynx	Men (118, 3057)	0–20 g/day	1.0	–	RR adjusted for smoking, age and area of residence; 95% CI from paper
		21–40 g/day	0.9	0.3–2.7	
		41–80 g/day	1.5	0.6–3.9	
		81–120 g/day	5.1	2.1–12.4	
		>121 g/day	10.6	4.4–25.8	

[a] g = pure ethanol
[b] Confidence intervals, calculated by the Working Group, when possible, unless otherwise specified

Table 49. Summary of results of case-control studies on oral cavity and pharyngeal cancer combined

Place (reference) Site	Subjects (cases, controls)	Total alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
USA, New York (Keller & Terris, 1965) Tongue, floor of mouth, palate, mesopharynx, hypopharynx, other parts of mouth, multiple sites	Men (134, 134)	Never <9.5 g/day 9.5–35 g/day >38g/day	1.0 1.4 2.1 3.7	– 0.6–3.0 0.9–4.8 1.7–7.8	RR calculated by Working Group on the basis of pairs matched for smoking
USA, New York (Feldman *et al.*, 1975; Feldman & Boxer, 1979) Oral cavity, pharynx	Men (96, 182)	None <70 g/day 71–138 g/day >140 g/day	1.0 0.6 2.1 4.5		RR adjusted for age and tobacco; 95% CI could not be calculated; test for trend significant at $\alpha = 0.005$ level

[a] g = pure ethanol
[b] Confidence intervals, calculated by the Working Group

In the USA, Keller and Terris (1965) investigated the smoking and drinking histories of 598 male cases of histologically confirmed squamous-cell carcinoma of the oral cavity and pharynx admitted to three Veterans Administration hospitals in New York during the period 1953-63. A similar number of male controls was selected individually as the next admission to the same hospital from persons in the same five-year age group. Information on alcohol and tobacco consumption was abstracted from clinical records based on data that had been elicited routinely by the admitting physicians. The contributions from different alcoholic beverages were summarized as daily intake of ounces of ethanol. After matching for smoking, the RR increased with increasing ethanol consumption in 134 case-control pairs. Rothman (1978) reported that the RR was higher for cancers at various sites in the mouth and mesopharynx than for cancer of the hypopharynx in heavy drinkers (>1.6 oz [>38 g] ethanol/day).

Feldman *et al.* (1975) and Feldman and Boxer (1979) compared the characteristics of a group of 185 male patients with cancers of the head and neck and a control group of 319 patients with other types of cancer admitted to five hospitals in New York City from 1971 to 1973. Only 182 male patients with cancers unrelated to tobacco and alcohol were eventually included in the control group. Information on dietary, smoking and drinking habits during the period five years before diagnosis was obtained by personal interview. The RRs for head and neck cancer were significantly related to alcohol consumption; when the comparison was restricted to the 96 males with cancer of the oral cavity, mesopharynx and hypopharynx, the increasing RR with increasing amount of daily alcohol drinking after adjustment for age and tobacco use became even more pronounced.

(iv) *Risk associated with type of alcoholic beverage*

In retrospective cohort studies of alcoholics, it has generally not been possible to distinguish the effects of different types of beverages. There was, however, a significantly increased risk for cancer of the pharynx (RR, 2.1; 95% CI, 1.0-3.7), but not for cancer of the oral cavity (RR, 1.4; 95% CI, 0.8-2.4), among beer-drinking Danish brewery workers (Jensen, 1979, 1980).

Wynder *et al.* (1957a) examined the dose-response relationships for whisky and beer drinking separately in male cases of oral cavity and pharyngeal cancer. For each type of beverage, an increasing trend was seen with increasing daily alcohol consumption after adjustment for smoking. The RR was highest among whisky drinkers of seven units [~ 65 g ethanol] or more per day, but the RRs for consumers of beer, wine and whisky were not substantially different for 1-6 units of ethanol intake. [The Working Group noted that no adjustment was made for consumption of other beverages.]

Increased RRs, unadjusted for smoking, were also observed by Keller and Terris (1965) for consumers of different types of alcoholic beverages compared with nondrinkers [wine only: RR, 2.5, 95% CI, 1.3-5.1; beer only: 2.6, 1.7-4.0; whisky only: 3.3, 2.1-5.1; mixed drinking: 2.7, 1.9-3.9]. Williams and Horm (1977) found similar patterns of RR controlled for smoking for equivalent lifetime consumption of beer and spirits among male cases of cancers of the lip and tongue, gum and mouth. The RRs for pharyngeal cancer were higher for those who drank wine and beer. The pattern among women was more uneven, possibly due to smaller numbers. [The Working Group noted that no adjustment was made for use of other alcoholic beverages in these two studies.]

(v) *Studies of joint exposure*

Tobacco smoking is causally related to cancer of the oral cavity and pharynx (IARC, 1986a), and alcohol and tobacco consumption are often correlated.

Rothman and Keller (1972) and Rothman (1976) reanalysed the information on consumption of alcohol and tobacco obtained by Keller and Terris (1965) in their study of US veterans. Altogether, 483 cases and 447 controls remained after exclusion of persons for whom there was inadequate information on either smoking or alcohol consumption. When stratifying for smoking, the RR for oral and pharyngeal cancer increased with increasing alcohol consumption at every level of smoking (Table 50). Persons with a daily consumption of ≥1.6 oz [36 g] ethanol had a two- to six-fold increased risk compared with nondrinkers.

Table 50. Relative risks[a] for oral cavity and pharyngeal cancer according to level of exposure to smoking and alcohol[b]

Ethanol/day (g)	Smoking (cigarette equivalents/day)			
	0	<20	20–39	40+
0	1.0	1.6	1.6	3.4
<9.5	1.7	1.9	3.3	3.4
9.5–35	1.9	4.9	4.8	8.2
>37	2.3	4.8	10.0	15.6
Cases/controls	26/85	66/97	248/197	143/68

[a]Risks are expressed relative to a risk of 1.0 for persons who neither smoked nor drank.
[b]From Rothman (1976)

The analysis showed a greater than multiplicative effect between alcohol and tobacco in the development of oral cavity and pharyngeal cancer, and heavy drinkers who were also heavy smokers had a RR of 15.6 when compared with persons who neither smoked nor drank. These results are in agreement with the findings of Wynder *et al.* (1957a), while Graham *et al.* (1977) found an additive effect of smoking and drinking. Elwood *et al.* (1984) could not distinguish statistically between an additive and a multiplicative effect. In the small Danish study of hypopharyngeal cancer (Olsen *et al.*, 1985a), a multiplicative effect was indicated. In the study of Tuyns *et al.* (1988), there was a multiplicative effect of alcohol and tobacco use on the risk of hypopharyngeal/epilaryngeal cancer (Table 51).

(iv) *Effect of alcohol in nonsmokers*

Some investigators have been able to evaluate the risk of oral cavity and pharyngeal cancer associated with alcohol drinking in nonsmokers. Wynder *et al.* (1957a) found no

Table 51. Relative risk for cancer of the hypopharynx/epilarynx according to level of exposure to smoking and alcohol[a]

Ethanol/day (g)	No. of cigarettes/day			
	0–7	8–15	16–25	26+
0–40	1.0	4.7	13.9	4.9
41–80	3.0	14.6	19.5	18.4
81–120	5.5	27.5	48.3	37.6
≥121	14.7	71.6	67.8	135.5
Total no. of cases	32	108	177	92

[a]From Tuyns *et al.* (1988)

difference in drinking habits among 16 cases of oral cavity and pharyngeal cancer and nine controls who did not smoke. By contrast, a doubling of the RR was seen among nonsmokers (26 cases, 85 controls) who consumed 1.6 oz or more [>37 g ethanol] alcohol per day compared to nondrinkers (Rothman & Keller, 1972; Rothman, 1976). Elwood *et al.* (1984) found a significant positive trend with alcohol intake in nonsmokers when the risk was examined for cancers of the oral cavity, pharynx and extrinsic larynx combined. In the study of Tuyns *et al.* (1988), there were more consumers of 80 g or more of ethanol per day among lifelong nonsmoking cases than among nonsmoking controls. [The Working Group noted that, in these studies, it is usually not possible to distinguish between current nonsmokers and lifelong nonsmokers.]

(*c*) *Cancer of the larynx*

The various subsites of the larynx must be distinguished from the point of view of degree of potential exposure: the endolarynx is exposed to inhaled agents, while the junctional area between the larynx and the pharynx is exposed to both inhaled and ingested agents. According to the ICD, these borderline areas (i.e., epiglottis free border, posterior surface of suprahyoid portion, junctional region of the three folds, aryepiglottic fold, arytenoid) should be classified partly under 161 (larynx) and partly under 146 and 148 (pharynx). In few studies is it stated whether these anatomical sites are included within the larynx. In some studies, the term 'extrinsic' and 'intrinsic' larynx are used, without specifying the subunits included.

(i) *Cohort studies* (descriptions of studies of cancers at many sites are given on pp. 158-164)

Studies of alcoholics have invariably shown increased risks for laryngeal cancer in comparison with the general population. The results of these studies are summarized in Table 52. It has not been possible to take into account the possible influences of differences

Table 52. Relative risks for laryngeal cancer in cohort studies

Study and reference	Number of subjects	Relative risk	95% CI[a]	Comments
Norwegian Alcoholics (Sundby, 1967)	5 deaths	3.1	[1.0-7.3]	Compared with Oslo inhabitants
Finnish Alcoholics (Hakulinen *et al.*, 1974)	3 cases	1.4	[0.3-4.1]	
Massachusetts Alcoholics (Monson & Lyon, 1975)	6 deaths	3.8	[1.4-8.2]	
US Veterans Alcoholics (Robinette *et al.*, 1979)	11 deaths	1.7	0.7-4.4	90% CI
Danish Brewery Workers (Jensen, 1980)	45 cases[b]	2.0	1.4-2.7	Cohort members drank on average four times more beer than reference population
Canadian Alcoholics (Schmidt & Popham, 1981)	12 deaths	4.3	[1.4-4.9]	Compared with Ontario population
		4.5	[2.3-7.8]	Compared with US veterans

[a] Confidence interval; [ ] when calculated by the Working Group
[b] Includes one case of cancer of the trachea

in smoking habits, which would have been desirable since tobacco smoke causes laryngeal cancer (IARC, 1986a). However, Schmidt and Popham (1981) found a SMR of 4.5 when they compared the number of laryngeal cancer deaths among Canadian alcoholics, who smoked on average 28 cigarettes per day, with that among of US veterans who smoked similar numbers of cigarettes per day. [The Working Group noted that other factors may vary between the two cohorts.] In Danish brewery workers (Jensen, 1980), the SIR for laryngeal (and tracheal) cancer was 3.7 [95% CI, 2.4-5.6] in persons with at least 30 years of employment in beer production, while it was 0.7 [0.04-8.7] in the small group of workers employed in mineral-water production.

These studies corroborate observations from occupational statistics (Young & Russell, 1926; Kennaway & Kennaway, 1947; Versluys, 1949) and clinical studies (Ahlbom, 1937; Jackson & Jackson, 1941; Kirchner & Malkin, 1953) of an association between laryngeal cancer and occupations with easy access to alcoholic beverages and with heavy alcohol drinking.

(ii) *Case-control studies*

The results of case-control studies on laryngeal cancer are summarized in Table 53. As part of a study of patients with cancers of the upper digestive tract and respiratory tract, Wynder *et al.* (1956) compared the smoking and drinking habits of 209 white male laryngeal cancer

Table 53. Summary of results of case-control studies on laryngeal cancer and alcohol consumption

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
USA, New York (Wynder *et al.*, 1956)	Men (209, 209)	Never or <1 unit[c]/day of mainly straight whisky	1.0	-	RR adjusted for smoking, calculated by the Working Group
		1-6 units/day	1.8	0.9-3.2	
		7+ units/day	5.3	2.5-11.2	
		Beer or wine, irrespective of amount consumed	1.8	1.0-2.9	
USA, Buffalo (Vincent & Marchetta, 1963)	Men (23, 100)	<47 g/day	1.0	-	Crude RR calculated by the Working Group
		≥47 g/day	5.9	2.4-14.3	
USA, Multicenter (Wynder *et al.*, 1976)	Men (224, 414)	<1 unit/day [~10 g]	1.0	-	RR adjusted for smoking, calculated by the Working Group
		1-6 units/day [~10-60 g]	1.2	0.8-1.9	
		7+ units/day [>60 g]	2.3	1.5-3.4	
France (Spalajkovic, 1976)	Men[b] (200, 200)	Nondrinkers	1.0	-	Crude RR calculated by the Working Group
		Drinkers	11.2	6.9-18.2	
USA, Multicenter (Williams & Horm, 1977)	Men (99, 1788)	Nondrinkers	1.0	-	RR adjusted for smoking, age and race; 95% CI could not be calculated
		<50 oz-year	2.2	$p < 0.05$	
		≥51 oz-year	2.3	$p < 0.05$	
	Women (11, 3188)	Nondrinkers	1.0	-	95% CI could not be be calculated
		<50 oz-year	0.3	NS	
		≥51 oz-year	0.8	NS	
USA, Washington State (Hinds *et al.*, 1979)	Men (47, 47)	<1 unit[d]/day	1.0	-	Crude RR
		1-2 units/day	2.1	0.7-6.3	
		3-6 units/day	3.8	1.3-10.9	
		>6 units/day	9.0	2.4-34.1	
Canada, Ontario (Burch *et al.*, 1981)	Men (184, 184)	<1.04 oz [24 g]/day	4.4	2.2-8.5	RR adjusted for smoking; 90% CI
		1.04-2.5 oz [24-58 g]/day	3.9	2.1-7.3	
		≥2.6 oz [≥60 g]/day	4.8	2.3-9.9	

Table 53 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
Ireland, Dublin (Herity et al., 1981)	Men (59, 200)	Nondrinkers	1.0		Crude RR; 95% CI could not be calculated
		Light drinkers	0.6		
		Heavy drinkers	3.2		
Canada, British Columbia (Elwood et al., 1984)	Men and women (154, 154)	Extrinsic larynx			RR adjusted for smoking, socio-economic group, marital status, dental care and history of tuberculosis; 95% CI could not be calculated
		<1 oz [24 g]/week	1.0		
		1–4 oz [24–96 g]/week	1.7		
		5–9 oz [120–216 g]/week	2.6		
		10–20 oz [240–480 g]/week	5.1		
		>20 oz [>480 g]/week	6.4		
		Intrinsic larynx			
		<1 oz [24 g]/week	1.0		
		1–4 oz [24–96 g]/week	1.1		
		5–9 oz [120–216 g]/week	0.7		
		10–19 oz [240–480 g]/week	2.0		
		≥20 oz [≥480 g]/week	2.2		
Denmark (Olsen et al., 1985b)[e]	Men and women (326, 1134)	0–100 g/week	1.0		RR adjusted for age and tobacco; 95% CI could not be calculated
		101–200 g/week	1.5		
		201–300 g/week	3.2		
		≥301 g/week	4.1		
USA, New Haven, CT (Zagraniski et al., 1986)	Men (87, 153)	Never	1.0	–	RR adjusted for smoking
		Ever	4.2	1.4–12.4	
France, Paris (Brugère et al., 1986)	Men (224, unk.)	Supraglottis			RR adjusted for smoking; control group selected from national survey
		0–39 g/day	1.0	–	
		40–99 g/day	2.6	1.3–5.1	
		100–159 g/day	11.0	5.5–21.7	
		≥160 g/day	42.1	20.5–86.4	
	(242, unk.)	Glottis + subglottis			
		0–39 g/day	1.0	–	
		40–99 g/day	0.8	0.5–1.2	
		100–159 g/day	1.5	0.9–2.6	
		≥160 g/day	6.1	3.4–10.9	

Table 53 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
France, Italy, Spain, Switzerland (Tuyns *et al.*, 1988)	(727, 3057)	Endolarynx			
		0–20 g/day	1.0	–	RR adjusted for smoking, age, area of residence
		21–40 g/day	0.9	0.7–1.3	
		41–80 g/day	1.1	0.8–1.5	
		81–120 g/day	1.7	1.2–2.4	
		>121 g/day	2.6	1.8–3.6	

[a] g = pure ethanol
[b] Confidence intervals, calculated by the Working Group, when possible
[c] 1 unit = 8 oz beer [9.5 g pure ethanol], 4 oz wine [12 g] or 1 oz whisky [9.5 g]
[d] 1 unit = 12 oz beer [14.3 g pure ethanol], 4 oz wine [12 g] or 1 oz spirits [9.5 g]
[e] Includes hypopharynx

patients with those of 209 hospital controls matched for age, sex, hospital status and educational and/or religious status. Information was obtained by personal interview without knowledge of the patient's case-control status. The laryngeal cancer patients had a significantly higher alcohol consumption than the control patients. When the comparisons were restricted to the group of patients who smoked 16-34 cigarettes per day, whisky drinkers consuming seven or more units per day had a 9.7-fold increase in risk compared with nondrinkers. After adjustment for smoking, the RR increased with increasing amount of whisky. There was no significant difference in the amounts of alcohol consumed by patients with intrinsic and extrinsic laryngeal cancer. Among 14 female laryngeal cancer cases, alcohol consumption was reported to be similar to that of controls. [The Working Group noted that some of the tumours classified as of the extrinsic larynx might have been of the hypopharynx.]

Schwartz *et al.* (1962; see description, p. 167) found a significantly higher average total ethanol consumption among 249 male laryngeal cancer cases (146 mg/day [115 g/day]) than among 249 accident controls (132 ml/day [104 g/day]); control patients with cancers unrelated to alcohol or tobacco use had an average daily consumption of 113 ml [89 g]. When the comparison was restricted to workers living in the département of Seine, the 63 laryngeal cancer patients had a significantly higher consumption (160 ml [126 g]/day) than the cancer controls (119 ml [94 g]/day) after accounting for differences in age and tobacco consumption.

In a study of patients with cancer of the oral cavity, pharynx or larynx, Vincent and Marchetta (1963) found increased consumption of both alcohol and tobacco among 23 male laryngeal cancer patients as compared with 100 controls selected from the gastrointestinal clinic of the same hospital that gave rise to the cases and in the same age groups. [The Working Group calculated a significant crude RR of 5.9 for consumers of 2 oz [47 g] or more ethanol per day compared with those taking less than 2 oz ethanol per day.]

Wynder *et al.* (1976) also reported RRs for smoking and drinking habits among 224 laryngeal cancer patients from different US hospitals and among 414 controls. Controls were matched to cases by year of interview, hospital status and age at diagnosis. Information on drinking and smoking was obtained by personal interview. There was a significant dose-response relationship for the amount taken per day after adjustment for smoking.

In France, Spalajkovic (1976) compared the alcohol consumption of 200 patients with cancer of the larynx or hypopharynx with that of 200 patients with nonmalignant ear, nose and throat disease. A significant increase in risk was noted for drinkers compared with nondrinkers.

In a study based on the Third National Cancer Survey in the USA (see description, pp. 170-171), significantly increased RRs were noted for alcohol drinking among 99 male laryngeal cancer patients after adjustment for smoking, age and race. No such increase was noted in women (11 cases; Williams & Horm, 1977).

Hinds *et al.* (1979) studied 47 laryngeal cancer cases in Washington State, USA, and 47 neighbourhood controls matched for sex, race and ten-year age group. Exposure information was obtained by interview. The RR for laryngeal cancer increased with increasing alcohol consumption.

In Ontario, Canada, 184 male laryngeal cancer cases were interviewed personally at home on smoking and on alcohol consumption, and on certain occupational exposures, and compared with 184 neighbourhood controls matched for age. Significantly increased RRs were noted for all categories of drinkers compared with nondrinkers. No dose-response relationship was apparent (Burch *et al.*, 1981).

Fifty-nine male laryngeal cancer cases were included in a study of head and neck cancer in Dublin, Ireland (Herity *et al.*, 1981), and their smoking and drinking habits were compared with those of 200 age-matched controls who were at the same hospital with cancers unrelated to smoking or with benign conditions. The RR was 3.2 among drinkers of more than 60 g ethanol per day for ten years, compared with nondrinkers and controlling for tobacco use.

In a study of cancers of the oral cavity, pharynx and larynx in British Columbia, Canada (see description, p. 171), Elwood *et al.* (1984) included 154 cases (130 male, 24 female) of extrinsic and intrinsic laryngeal cancer. Their drinking and smoking habits were compared with those of 374 hospital controls with other cancers. For cancers of the extrinsic and the intrinsic larynx, significant dose-response relationships ($p = 0.001$ and $p = 0.05$, respectively) were observed for alcohol consumption when account was taken of smoking, socioeconomic group, marital status, dental care and history of tuberculosis.

In a case-control study nested within the Danish brewery worker cohort, nonsignificantly increased RRs were associated with moderate and heavy alcohol consumption (Adelhardt *et al.*, 1985). [The Working Group noted the small size of this study.]

In a population-based study which comprised all laryngeal cancer patients below the age of 75 years seen at five departments involved in laryngeal cancer therapy in Denmark between 1980-82, Olsen *et al.* (1985b) investigated 326 patients and 1134 controls. After adjustment for tobacco use, a significant dose-response relationship was seen with total alcohol consumption, measured in grams of ethanol per week.

Zagraniski *et al.* (1986) investigated the drinking habits of 87 white US male laryngeal cancer patients and 153 hospital controls with no prior diagnosis of cancer or respiratory disease. Controls were matched on hospital, year of admission, decade of birth, county of residence, smoking status and type of tobacco used. The case and control groups represented 59% and 48%, respectively, of the originally identified cases and controls. Various measures of alcohol consumption showed an increased RR after adjustment for residual differences in smoking habits between cases and controls.

In France, Brugère *et al.* (1986) (see description, p. 171) investigated 466 men with laryngeal cancer. Increasing RRs with increasing amount of ethanol consumed per day were noted for three different locations in the larynx (supraglottis, glottis, subglottis), and particularly for cancer of the supraglottis.

In the study by Tuyns *et al.* (1988) (see description, p. 172), there were 727 male cases of laryngeal cancer (426 supraglottic, 270 glottic and subglottic and 31 endolarynx not otherwise specified). When their drinking and smoking habits were compared with those of 3057 male population controls, a significantly increasing RR was seen with amount of ethanol drunk daily; the RR for cancer of the endolarynx when comparing consumption of

≥121 g/day *versus* 0-20 g/day was 2.6 (95% CI, 1.8-3.6). RRs were adjusted for smoking, age and area of residence.

(iii) *Risk associated with type of alcoholic beverages*

Studies have been carried out to investigate whether the ethanol concentrations of different alcoholic beverages entail different RRs for laryngeal cancer. In retrospective cohort studies, it has generally not been possible to distinguish the effects of different types of beverage; however, a significantly increased risk was noted among brewery workers with an above-average beer consumption (Jensen, 1980).

Wynder *et al.* (1956) found the RR to be particularly high for 'heavy' whisky consumers in the USA, but a significant RR [1.7, after adjusting for smoking] was also seen for wine and beer drinking; no difference was found with regard to drinking whisky diluted or undiluted. In a later study in the USA (Wynder *et al.*, 1976), no difference in predominant type of alcoholic beverage was seen between cases and controls, and, in a study based on the Third National Cancer Survey Study, similar RRs were observed with equivalent lifetime consumption of wine, beer and spirits (Williams & Horm, 1977). In Canada, too, the RRs were similar for consumption of comparable amounts of beer and spirits in terms of daily ethanol intake (Burch *et al.*, 1981). In Denmark (Olsen *et al.*, 1985b), the only significantly increased RR was found for drinking beer as the preferred type of alcohol, and the RRs for drinking wine and spirits were not increased. [The Working Group noted that in none of these studies was adjustment made for use of other beverages.]

(iv) *Studies of joint exposure*

An extensive analysis and discussion of the joint effect of alcohol and tobacco is provided by Flanders and Rothman (1982) and by Walter and Iwane (1983), who reanalysed data from the study of Williams and Horm (1977). They restricted the analysis to 87 male cases and 956 male controls with cancers not related to alcohol use, tobacco use or certain occupational exposures; information was also available on age, sex and alcohol and tobacco use. Flanders and Rothman (1982) also reanalysed the data previously reported by Wynder *et al.* (1976), restricting the analysis to 224 male cases and 414 male controls for whom information on both alcohol use and tobacco use was available. The results point to a multiplicative rather than an additive effect, but neither data set is sufficiently extensive to allow a conclusion. Similar limitations apply to two Canadian studies (Burch *et al.*, 1981; Elwood *et al.*, 1984). In the study of Tuyns *et al.* (1988), a multiplicative model provided an adequate description of the data (see Table 54). Other investigators have reported synergism between alcohol and tobacco in the induction of laryngeal cancer (Hinds *et al.*, 1979; Herity *et al.*, 1981, 1982; Olsen *et al.*, 1985b; Zagraniski *et al.*, 1986).

(v) *Effect of alcohol in nonsmokers*[1]

Flanders and Rothman (1982) analysed data from Wynder *et al.* (1976) regarding the drinking habits of nonsmokers and found that there were no drinkers among the five cases

[1]Subsequent to the meeting, the Secretariat became aware of a further study demonstrating an association between laryngeal cancer and alcohol drinking in lifetime nonsmokers (Brownson & Chang, 1987).

Table 54. Relative risks for cancer of the endolarynx, according to level of exposure to smoking and alcohol[a]

Ethanol/day (g)	Cigarettes/day			
	0–7	8–15	16–25	26+
0–40	1.0	6.7	12.7	11.5
41–80	1.7	5.9	12.2	18.5
81–120	2.3	10.7	21.0	23.6
≥121	3.8	12.2	31.6	43.2
Total no. of cases	50	147	357	173

[a]From Tuyns et al. (1988)

of laryngeal cancers in nonsmokers. [The Working Group calculated that 1.4 would have been expected on the basis of information for 84 controls.] Burch *et al.* (1981) observed a positive trend in RR with amount of alcohol consumed among lifetime nonsmokers: 7.7 in the highest consumption category (≥2.6 oz [≥60 g] ethanol) compared with nondrinkers. Elwood *et al.* (1984) also found a positive trend with alcohol use in nonsmokers when the risk was examined for cancers of the oral cavity, pharynx and larynx combined. Tuyns *et al.* (1988) found no difference between observed and expected numbers of drinkers among lifelong nonsmokers with cancer of the endolarynx.

(*d*) *Cancer of the oesophagus*

(i) *Cohort studies* (descriptions of studies of cancer at many sites are given on pp. 158-164.)

Almost all of the retrospective cohort studies of persons with an above average intake of alcohol have shown an approximately two-fold increased risk for cancer of the oesophagus compared with rates for the general population (Table 55). In these studies, no information was available on tobacco smoking or other risk factors (e.g., poor diet), which may influence the risk for oesophageal cancer. In the study of Canadian alcoholics (Schmidt & Popham, 1981), the members had an average daily tobacco consumption of 28 cigarettes. The SMR was only marginally affected (2.3) when the observed number of oesophageal cancer deaths was compared with an expected number derived from the death rates for smokers of similar numbers of cigarettes per day in the prospective study of US veterans. [The Working Group noted that it must be assumed that the cohorts studied had rather extreme smoking patterns in order to explain the two-fold increase in risk compared with that of a background population (Axelson, 1978).]

The large Japanese study is the only prospective cohort study in which information is provided on the RR for oesophageal cancer in relation to alcoholic beverage. After

Table 55. Relative risks for oesophageal cancer in cohort studies

Study and reference	Number of subjects	Relative risk	95% CI[a]	Predominant beverage	Comments
Norwegian Alcoholics (Sundby, 1967)	40 deaths	4.1	[2.9–5.6]	Unknown	Compared with Oslo population
Finnish Alcohol Misusers (Hakulinen et al., 1974)	101 cases	1.7	[1.4–2.1]	Unknown	
Finnish Alcoholics (Hakulinen et al., 1974)	4 cases	4.1	[1.4–9.3]	Unknown	
Massachusetts Alcoholics (Monson & Lyon, 1975)	5 deaths	1.9	[0.4–5.5]	Unknown	
Dublin Brewery Workers (Dean et al., 1979)	10 deaths	0.6	[0.3–1.2]	Beer	Based on Dublin rates
Japanese Prospective Study (Hirayama, 1979)	297 deaths	1.1 1.2 1.7 2.0	–	Beer Saké Whisky Shochu	Adjusted for tobacco, age and sex; RRs calculated by the Working Group
US Veterans Alcoholics (Robinette et al., 1979)	13 deaths	2.03	0.9–5.1	Unknown	
DAnish Brewery Workers (Jensen, 1980)	41 cases	2.1	1.5–2.8	Beer	Four times higher beer consumption in cohort than in reference population
Canadian Alcoholics (Schmidt & Popham, 1981)	16 deaths	3.2	[1.8–5.2]	Unknown	Compared with Ontario population
		2.3	[1.3–3.8]		Compared with US veterans

[a]Confidence interval; [ ] when calculated by the Working Group

adjustment for smoking, increased SMRs of 1.7 and 2.0 [calculated by the Working Group] were noted for whisky and *shochu* drinking, respectively (Hirayama, 1979).

(ii) *Case-control studies*

The risk for oesophageal cancer in relation to various total alcohol intakes, the effect of various alcoholic beverages, and interactions with tobacco and nutrition have been quantified in several case-control studies. The results are summarized in Table 56.

Wynder and Bross (1961) studied 150 men with squamous-cell carcinoma of the oesophagus and 150 hospital controls matched for age and sex, primarily with cancer (64%) but excluding smoking-related diseases. Information was obtained by personal interview, in most cases conducted without knowledge of the diagnosis. The oesophageal cancer patients took significantly more drinks per day than the controls, and a dose-response relationship was apparent. A clear dose-response relationship was seen with increasing amounts of whisky and beer consumed daily when the analysis was restricted to smokers of 16-34 cigarettes per day.

Schwartz *et al.* (1962) (see description, p. 167) found that average total alcohol consumption was significantly higher among 362 oesophageal cancer patients (154 ml [122 g] ethanol per day) than among 362 accident controls (136 ml [107 g] ethanol per day) after adjustment for tobacco use. A higher proportion of cases than controls had symptoms of alcoholism. The average difference between cases and cancer controls (113 ml [89 g] ethanol per day) was even higher and remained significant after adjusting for smoking. When the comparison was restricted to workers living in the département of Seine, the 100 oesophageal cancer patients had a significantly higher consumption (157 ml [124 g]/day) than the cancer controls (119 ml [94 g]/day) after accounting for differences in age and tobacco consumption.

In Puerto Rico, Martinez (1969) studied 179 cases (120 male, 59 female) of squamous cell-carcinoma of the oesophagus and 537 controls (360 male, 177 female) matched for age and sex (see description, p. 170). When the independent effect of alcohol consumption was examined by additional matching on tobacco (111 male and 52 female pairs), a clear dose-response relationship was seen in men, even after adjusting for smoking, while no association was apparent in women. [The Working Group noted that only four female cases and four controls consumed two or more units of ethanol/day.]

Two studies of oesophageal cancer in African male cases and hospital controls without cancer in South Africa showed no association with consumption of alcoholic beverages when adjustment was undertaken for smoking habits. Men in Durban had a RR of 0.9 (Bradshaw & Schonland, 1969) and men in Johannesburg a RR of 1.0 (Bradshaw & Schonland, 1974). [RRs were calculated by the Working Group.]

As part of a larger study of various digestive tract cancers, 52 cases of oesophageal cancer in Minnesota, USA, were compared with 1657 hospital controls matched for age, sex, race and hospital to the whole series of digestive tract cancer cases. A significant crude association was found for consumption of beer and spirits but not of wine (Bjelke, 1973).

Table 56. Summary of results of case-control studies on oesophageal cancer and alcohol consumption

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
USA, New York (Wynder & Bross, 1961)	Men (150, 150)	Never	1.0	-	Crude RR calculated by the Working Group
		<1 unit/day	0.6	0.2-2.5	
		1-2 units/day	1.6	0.4-7.1	
		3-6 units/day	7.1	2.1-26.3	
		7-12 units/day	6.8	1.6-30.4	
		>12 units/day	5.0	1.1-22.6	
		Binges	12.5	1.5-78.4	
Puerto Rico (Martinez, 1969)	Men (111, 111)	None	1.0	-	Crude RR based on pairs matched on smoking, calculated by the Working Group
		<1 unit[c]/day	0.6	0.2-2.0	
		2-4 units/day	2.1	0.8-5.1	
		≥5 units/day	7.7	3.0-20.0	
	Women (52, 52)	None	1.0		
		<1 unit/day	1.9	0.5-6.9	
		≥2 units/day	1.1	0.3-4.6	
South Africa, Durban (Bradshaw & Schonland, 1969, 1974)	Men (98, 341)	Never	1.0		RR adjusted for smoking, calculated by the Working Group
		Ever	0.9	0.4-1.9	
South Africa, Johannesburg (Bradshaw & Schonland, 1974)	Men (196, 1064)	Never	1.0	-	RR adjusted for smoking, calculated by the Working Group; 95% CI from paper
		Ever	1.0	0.6-1.8	
USA, Minnesota (Bjelke, 1973)	Men, women (52, 1657)	Beer <1 time/month	1.0	-	RR adjusted for sex; RR for 6-13 times/months calculated as 2.9 by the Working Group
		1-5 times/month	0.7	0.3-1.9	
		6-13 times/month	2.7	1.2-6.8	
		≥14 times/month	4.4	2.3-8.3	
		Wine <1 time/month	1.0	-	
		1-5 times/month, 6-13 times/month, ≥14 times/month	0.5	0.2-1.2	
		Spirits <1 time/month	1.0	-	RR for 1-5 times/month calculated as 1.7 by the Working Group
		1-5 times per month	1.9	0.9-3.3	
		6-13 times/month	1.6	0.7-4.1	
		≥14 times/month	2.1	1.0-4.3	

Table 56 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
Singapore (De Jong et al., 1974)	Men (95, 165)	Never	1.0		Crude RR for samsu (strong liquor) drinking; significant dose-response remains after adjustments; 95% CI could not be calculated
		<daily	2.0		
		Daily	2.9		
USA, Multicenter (Williams & Horm, 1977)	Men (38, 1750)	Nondrinkers	1.0		RR adjusted for age, race and smoking; 95% CI could not be calculated
		<50 oz-year	0.9		
		≥51 oz-year	1.4		
	Women (19, 3169)	Nondrinkers	1.0		
		<50 oz-year	0.9		
		≥51 oz-year	8.1	$p < 0.05$	
France, Brittany (Tuyns et al., 1977)	Men (200, 778)	0-20 g/day	1.0		RR adjusted for smoking; 95% CI could not be calculated
		21-40 g/day	1.2		
		41-60 g/day	3.4		
		61-80 g/day	6.1		
		81-100 g/day	6.6		
		≥101 g/day	18.3		
France, Normandy (Tuyns et al., 1979)	Men (312, 869)	0 g/day	1.0		RR adjusted for smoking calculated by the Working Group; 95% CI could not be calculated
		1-40 g/day	0.8		
		41-80 g/day	2.3		
		≥81 g/day	11.6		
USA, Washington DC (Pottern et al., 1981)	Men (90, 213)	Never drank more than five glasses of alcoholic beverages/week for >1 month	1.0	-	Crude RR; RRs remain high after adjustment for smoking; 95% CI from paper
		1.0-5.9 oz [9.4-55 g]/day	4.0	1.4-12.0	
		6.0-14.9 oz [56-140 g]/day	5.5	2.0-15.0	
		15.0-29.9 oz [141-281 g]/day	7.6	2.7-22.0	
		30.0-80.6 oz [282-757 g]/day	7.5	2.5-22.0	

Table 56 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)	95% CI[b]	Comments
Uruguay, Montevideo (Vassallo *et al*. 1985)	Men (185, 386)	0–49 ml [39 g]/day	1.0	-	RR adjusted for age and tobacco smoking; 95% CI from paper
		50–99 ml [40–78 g]/day	3.8	2.4–6.2	
		≥100 ml [≥79 g]/day	7.6	4.5–12.8	
Southern Brazil (Victoria *et al*., 1987)	Men, women (171, 342)	Nondrinkers	1.0		*Cachaça* drinking; association persisted after adjustment for confounders; 95% CI could not be calculated
		1–29 g/day	3.5		
		30–89 g/day	6.3		
		90+ g/day	8.2		

[a] g = pure ethanol
[b] Confidence intervals, calculated by the Working Gorup, when possible, unless otherwise indicated
[c] 1 unit = 18 oz beer [21.4 g pure ethanol], 8 oz wine [24 g] or 2 oz spirits [19 g]

De Jong *et al.* (1974) investigated risk factors for oesophageal cancer among Chinese men in Singapore, comparing 95 cases with 465 hospital controls. Significantly elevated RRs were associated with intake of *samsu* (a form of spirits reported by the authors to have an alcohol content equivalent to that of whisky), but not with intake of other spirits. A significant dose-response relationship for *samsu* drinking persisted after adjustment for other identified risk factors, including smoking.

In the study based on the Third National Cancer Survey in the USA (see description, pp. 170-171), Williams and Horm (1977) found nonsignificantly increased RRs among men with oesophageal cancer, but a significant risk (8.1) among women who were classified as heavy drinkers, after controlling for smoking.

Two case-control studies of oesophageal cancer in relation to alcohol and tobacco consumption, as well as to diet, were carried out in a high-incidence area for this cancer in northwestern France (Tuyns, 1970). Aspects of the design of the studies, consumption patterns and selection of control groups have been reported in several papers (Péquignot & Cubeau, 1973; Tuyns & Massé, 1975; Jensen *et al.*, 1978; Tuyns *et al.*, 1983). In the first study, alcohol and tobacco consumption were compared for 200 male cases of oesophagea cancer representative of all cases in the population between 1972 and 1974 and for 77[illegible] controls selected randomly from the same population. After adjustment for age and smoking, a clear increase in RR was seen with total amount of alcohol consumed per day expressed as grams of ethanol derived from different types of alcoholic beverages, adjustment for smoking did not substantially affect the crude risk estimates (Tuyns *et al.*, 1977). In the second study of 743 cases of oesophageal cancer (704 male, 39 female) and 197 controls chosen at random from the population (923 male, 1053 female) of Normandy, a significantly increased RR (2.7) was observed for any type of alcohol consumption (Tuyns *et al.*, 1982). In a preliminary analysis of information for 312 male cases and 869 hospita based controls (excluding persons with smoking- and alcohol-related diseases), a clear dose-response relationship was seen (Tuyns *et al.*, 1979). This was sustained by the fir[illegible] detailed report of the full study in which all cases and population controls are compare[illegible] The study also showed an association between risk for oesophageal cancer and poor diet, on the basis of an index incorporating citrus fruit, meat and vegetable oils. The risk associat[illegible] with alcohol intake was independent of poor diet (Tuyns *et al.*, 1987).

Pottern *et al.* (1981) studied black men in Washington DC, USA, who had died from oesophageal cancer in 1975-77. Information was obtained for 120 cases (response rate, 67[illegible] and 250 controls (response rate, 71%) by personal interviews with next-of-kin; about 20% did not provide quantitative information on alcohol intake. Estimates of total ethanol intake were made by combining levels in various beverages. Significantly increased R[illegible] were seen for alcohol drinkers when compared with nondrinkers, and a dose-response relationship emerged. A further analysis of this study (Ziegler, 1986) also showed [illegible] relationship with low consumption of various foods and nutrients. The risks associated w[illegible] alcohol intake and dietary status remained distinct.

All patients admitted to the Oncology Institute of Montevideo, Uruguay, w[illegible] interviewed with regard to past and current consumption of alcohol, tobacco and m[illegible] (Vassallo *et al.*, 1985). Between 1979 and 1984, there were 226 cases (185 male, 41 female) o oesophageal cancer, for whom 469 controls (386 male, 83 female) with other neoplastic conditions were selected. There was a significant positive trend with daily intake of spirits in men after adjustment for age and smoking. No data were given for women.

In southern Brazil, 171 histologically confirmed cases of squamous-cell carcinoma of the oesophagus were compared with twice as many individually matched (age, sex, hospital) hospital controls, excluding patients with diseases related to alcohol and tobacco (Victoria *et al.*, 1987). Cases and controls were personally interviewed with regard to consumption of alcohol, tobacco, hot beverages and several foodstuffs. There was an important association with consumption of alcoholic beverages. This was seen in particular for drinking of *cachaça*, a distilled sugar cane spirit which is the most common alcoholic drink in that part of Brazil where it accounts for approximately 80% of alcohol consumption. There were also significant associations with lifetime consumption of beer and wine. The significant association with daily intake and years of drinking *cachaça* persisted after taking account of place of residence, smoking and fruit and meat eating in a logistic regression analysis.

(iii) *Risk associated with type of alcoholic beverage*

In retrospective cohort studies of alcoholics it has generally not been possible to distinguish the effects of different types of beverages; however, in the two studies of brewery workers (Dean *et al.*, 1979; Jensen, 1980), there was evidence that beer was the predominant beverage consumed. The study of Dublin brewery workers showed no increased risk, while the study of Danish brewery workers with high daily beer consumption showed a significant, two-fold risk.

Wynder and Bross (1961) indicated that the RR increased particularly steeply in whisky drinkers, but beer and wine drinkers were also at increased risk for oesophageal cancer. [The Working Group noted that a high RR (6.4) was seen in the category of >6 units of whisky per day, but the average consumption is not given; no adjustment was made for use of other beverages.] In the study of Pottern *et al.* (1981), the RR was highest among consumers of spirits, but the RRs for consumption of beer and wine were compatible with those for spirits. Martinez (1969) found no difference in RR for consumers of commercial rum only, of home-processed rum only or of a mixture of beverages. Tuyns *et al.* (1979) found an indication that oesophageal cancer in Normandy was associated with consumption of all types of alcoholic beverages but noted that the association might be stronger for consumers of distillates of apple cider (approximately 400 g ethanol per l) and of cider itself (approximately 40 g ethanol per l) than for those drinking wine and beer when account was taken of both tobacco and total ethanol intake. In an extended analysis in which cases in Brittany were compared with population controls, beer, cider and wine had the strongest influence on risk, but it could not be ruled out that all types of beverages contributed to the risk in proportion to their alcohol content (Breslow & Day, 1980).

(iv) *Studies of joint exposure*

Tobacco smoking is causally related to oesophageal cancer (IARC, 1986a). Ziegler (1986) found an independent effect of alcohol on oesophageal cancer risk after adjustment for several dietary factors. Similar results were reported from the large case-control study carried out in Normandy (Tuyns *et al.*, 1987), where adjustment for nutrition could not explain the increased risk due to alcohol consumption.

The joint actions of alcohol and tobacco and of alcohol and nutrition have been the subject of several analyses. In their studies in north-western France, Tuyns *et al.* (1977, 1979) found a combined effect of alcohol and tobacco, which they described as multiplicative (Table 57). Similar combined effects of alcohol consumption and nutrition in the causation of oesophageal cancer have been reported; after adjustment for tobacco, a 90-fold increased risk for oesophageal cancer was seen among persons who drank more than 120 g ethanol per day and had a low consumption of citrus fruits, meat and vegetable oils, in comparison with subjects who drank less than 40 g ethanol per day and had a high intake of fresh meat, citrus fruits and vegetable oils (Tuyns *et al.*, 1987).

(v) *Effect of alcohol in nonsmokers*

Tuyns (1983) found that the RR for oesophageal cancer among 39 male and 36 female oesophageal cancer patients who had never smoked increased considerably with increasing alcohol consumption; values were similar in men and women (Table 58).

(*e*) *Cancers of the stomach, colon and rectum*

(i) *Cohort studies* (descriptions of studies of cancers at many sites are given on pp. 158-164).

In general, adjustment for any confounding effects of diet has not been possible in the cohort studies considered below. Dietary factors are thought to be involved in the etiology of stomach cancer and of cancer of the large bowel (colon especially), and dietary habits are likely to vary with alcohol consumption. However, in most of these cohort studies, including the cohorts that were determined retrospectively, information on individual dietary habits was not collected. The studies are summarized in Table 59.

In the study of Norwegian alcoholics (Sundby, 1967), the number of deaths from colon cancer (9) closely matched the expected value (9.4). There was a nonsignificant excess of rectal cancer deaths (SMR, 1.9; 12 cases) and a nonsignificant increase in the risk for death from stomach cancer (SMR, 1.3; 45 cases) when comparison was made with the population of Oslo.

In the Finnish study of alcohol misusers and alcoholics (Hakulinen *et al.*, 1974), the observed number of colon cancer cases (82) within the misusers cohort was fewer than expected (86.6); data for stomach cancer were not reported. For the cohort of chronic alcoholics, the observed numbers of stomach cancers (six) and colon cancers (three) did not clearly differ from those expected (8.0 and 1.6, respectively). Data were not presented for rectal cancer in either cohort.

In the study of UK alcoholics (Adelstein & White, 1976), there were eight deaths from stomach cancer (10.2 expected), nine deaths from cancer of the small intestine and colon (6.8 expected) and four deaths from rectal cancer (4.3 expected).

In the study of alcoholics in Massachusetts (Monson & Lyon, 1975), the proportions of stomach and colorectal cancers were not significantly increased: 15 deaths from stomach

Table 57. Combined effect of alcohol and tobacco on relative risks for cancer of the oesophagus[a]

Ethanol/day (g)	Tobacco consumption/day (g)		
	0–9	10–19	≥20
0–40	1.0	3.4	5.1
41–80	7.3	8.4	12.3
≥81	18.0	19.9	44.4
Total no. of cases	78	58	64

[a] From Tuyns *et al.* (1977); risks are expressed relative to a risk of 1.0 for persons smoking <10 g/day and drinking ≤40 g/day.

Table 58. Relative risks (RR) for oesophageal cancer in relation to average daily alcohol consumption by nonsmoking males in Normandy, France[a]

Ethanol/day (g)	Males		Females	
	No. of cases	RR	No. of cases	RR
0–40	7	1.0	25	1.0
41–80	15	3.8	8	5.6
81–120	9	10.2	3	11.0
≥121	8	101.0	–	–

[a] From Tuyns (1983)

cancer, seven from colon cancer and four from rectal cancer were observed, whereas 14.6, 11.2 and 5.7 were expected, respectively.

In the Japanese prospective study (Hirayama, 1979), the SMR for death from stomach cancer (1917 deaths) in daily consumers of alcohol as compared with nondrinkers was 1.0 among men. Data are not given for women. Data on alcohol intake in relation to colon cancer (96 deaths) were not tabulated; however, data displayed in a graph indicate that male smokers who drank daily had about a 50% higher risk of intestinal cancer (colon plus small intestine) than smokers who did not drink alcohol; for rectal cancer, no such association was detected. In an earlier report of this study (Hirayama, 1977), the risk for colorectal cancer

Table 59. Relative risks for stomach, colon and rectal cancers in cohort studies

Study and reference	Stomach		Colon		Rectum		Comments
	No. of subjects	Relative risk (95% CI)	No. of subjects	Relative risk (95% CI)	No. of subjects	Relative risk (95% CI)	
Norwegian Alcoholics (Sundby, 1967)	45 deaths	1.3 (0.9-1.7)	9 deaths	1.0 (0.5-1.9)	12 deaths	1.9 2.9	Compared with Oslo population Compared with Norwegian population
Finnish Alcohol Misusers (Hakulinen et al., 1974)	-	-	82 cases	0.95 (0.7-1.1)	-	-	
Finnish Alcoholics (Hakulinen et al., 1974)	6 cases	0.8 (0.3-1.6)	3 cases	1.8 (0.4-5.4)	-	-	
Massachusetts Alcoholics (Monson & Lyon, 1975)	15 deaths	1.0 (0.6-1.7)	7 deaths	0.6 (0.3-1.3)	4 deaths	0.7 (0.2-1.8)	
UK Alcoholics (Adelstein & White, 1976)	8 deaths	0.8 (0.3-1.5)	9 deaths (intestine)	1.3 (0.6-2.5)	4 deaths	0.9 (0.3-2.4)	
Dublin Brewery Workers (Dean et al., 1979)	40 deaths	0.8 (0.6-1.1)	32 deaths	1.3 (0.9-1.9)	32 deaths	1.6 (1.1-2.3)	Compared with Dublin blue-collar workers
US Veterans Alcoholics (Robinette et al., 1979)	9 deaths	1.0 (90% CI, 0.4-2.3)	7 deaths	0.8 (0.3-1.9)	6 deaths	3.3 (0.7-22.4)	
Danish Brewery Workers (Jensen, 1980)	92 cases	0.9 (0.7-1.1)	87 cases	1.1	85 cases	1.0 (0.8-1.3)	Total cohort (brewers and mineral water bottlers)
Canadian Alcoholics (Schmidt & Popham, 1981)	19 deaths	1.0 (0.6-1.6) 1.7 (1.0-2.6)	19 deaths	1.0 (0.6-1.6) 1.0 (intestine) (0.6-1.6)	10 deaths	1.0 (0.5-1.9) 1.1 (0.5-2.0)	Compared with Canadian population Compared with US veterans smoking 21-39 cigarettes/day

was shown to be 1.7 times higher in daily beer drinkers than in nondrinkers. [The Working Group noted that statistical significance was not shown, and separate data were not presented for colon and rectal cancers.]

In the study of alcoholic US veterans (Robinette *et al.*, 1979), the SMR for death from stomach cancer (nine deaths) was 1.0. For colon cancer (seven deaths) and rectal cancer (six deaths), the SMRs were 0.8 and 3.3, respectively.

In the study of Danish brewery workers and mineral-water factory workers (Jensen, 1980), no increase in risk was observed for cancers of the stomach (RR, 0.9; 92 cases), colon and sigmoid (RR, 1.1; 87 cases) or rectum (RR, 1.0; 85 cases). There was no variation in risk for stomach, colon or rectal cancer in relation to duration of employment. [The Working Group noted that this study was designed specifically to examine the relationship between beer drinking and cancer of the large bowel.] The author noted that, if the results of this investigation are taken together with those obtained from the study of the Copenhagen Temperance Society, the risk for rectal cancer can be compared in groups with extreme differences in beer consumption, ranging from the low consumption of (or abstention from) beer in Seventh-day Adventists to the average intake of almost 2.5 l of beer per day for the brewery workers. Since in neither group does the risk for rectal cancer differ from that of the total population, the author concluded that these studies do not indicate a causal association between beer drinking and rectal cancer (Jensen, 1983).

In the study of Dublin brewery workers (Dean *et al.*, 1979), there were 40 deaths from stomach cancer, 32 deaths from cancer of the colon, and 32 from cancer of the rectum. Expected numbers were derived for blue-collar workers in Dublin, in order to control for socioeconomic class; the differences between the observed numbers and those expected for cancers of the stomach (49.2) and colon (24.1) were not significant, but for rectal cancer there was a significant excess of observed (32) to expected (19.7). [The Working Group noted that this study was designed specifically to examine the relationship between beer drinking and cancer of the large bowel.]

In order to to investigate this association further, the relatives of men who had died of rectal cancer were sought and were questioned about the drinking habits of the deceased. For each relative traced, two control relatives were sought from among men who had died of other causes in the same age group, matched for age at death and the year in which they died. It was possible to trace the relatives of 16 of the 32 who had died of cancer of the rectum, of whom 15 drank stout, and 29 of the 64 control relatives, of whom 27 drank stout. The mean alcohol intake of those who had died of cancer of the rectum was reported by the next-of-kin to have been 23.6 pints (13.4 l) of stout per week and 1.8 glasses (0.13 l) of spirits per week. The mean intake for the 29 controls was 16.1 pints (9.1 l) of stout per week and four glasses (0.28 l) of spirits per week. This difference is significant ($p < 0.05$) (Dean *et al.*, 1979). [The Working Group noted the high potential for bias in this comparison because of the low interview rates.]

In the study of Canadian alcoholics (Schmidt & Popham, 1981), the SMR for death from stomach cancer was 0.95 (19 deaths; not significant), that for colon cancer, 1.04 (19 deaths; not significant), and that for rectal cancer, 1.02 (10 deaths; not significant), in comparison with the general male population of Ontario. In comparison with veterans who smoked 21-39 cigarettes daily, the SMRs for cancers of the stomach, intestine and rectum became 1.7, 1.02 and 1.1, respectively. The authors postulate that the nonsignificant excess of stomach cancer deaths was 'probably attributable to a difference in the class composition of the two samples [alcoholics and veterans] rather than to a difference in their drinking habits'.

In the Kaiser-Permanente study (Klatsky *et al.*, 1981), neither stomach cancer (13 deaths) nor colorectal cancer (19 deaths) was associated with level of alcohol consumption.

In the Framingham study (Gordon & Kannel, 1984), there was a strong positive relationship between heavy consumption of alcohol and stomach cancer mortality for people of each sex (five deaths in women, 13 deaths in men). Multivariable analysis of this relationship, controlling for cigarette smoking, systolic blood pressure, age, relative weight and plasma lipoprotein profile, showed significant positive relationships for both women and men. There was no significant relationship between alcohol use and cancer of the colon (17 deaths in men, 19 in women). No data were reported for rectal cancer. [The Working Group noted that the use of standardized logistic regression coefficients precludes quantitative estimates of the relation between alcohol intake and cancer risk.]

In the study of Hawaiian Japanese (Pollack *et al.*, 1984), there were 99 incident cases of stomach cancer, 92 cases of colon cancer, and 62 cases of rectal cancer. There was no evidence of a relationship between alcohol consumption and stomach and colon cancers After adjusting for age and cigarette smoking, there was a significant trend ($p < 0.001$) for rectal cancer, with increasing incidence rates accompanying successively higher levels of alcohol consumption. [The Working Group calculated the RR for ≥40 oz/month (800 g) in comparison with abstainers to be 2.9.] In order to examine this relationship further, the authors estimated the risk for rectal cancer among subjects who consumed a given amount of each particular type of alcoholic beverage relative to the risk for those who did no consume the beverage at all, controlling for age, smoking and consumption of other types of alcohol. The only category for which the RR for rectal cancer was significantly raised wa the highest, consuming 500 oz (15 l) or more of beer per month; the RR for this category was 3.1 ($p < 0.01$). [The Working Group noted that point estimates for lower categories of beer intake are not given but can be derived from a figure presented in the paper a approximately 1.0 for 1-9 oz, 1.5 for 10-99 oz and 1.5 for 100-499 oz per month.]

In the study of Japanese doctors (Kono *et al.*, 1986), age- and smoking-standardized rates for death from stomach cancer (116 deaths) and colorectal cancer (sites combined; 3[illegible] deaths) were not clearly related to alcohol consumption category; rates for these cancers were 10-40% higher (not statistically significant) in occasional and daily drinkers than i nondrinkers.

Wu *et al.* (1987) studied a cohort of 11 888 residents of a retirement community in California, USA. Consumption of alcoholic beverages on an average weekday was assessed by a self-administered questionnaire for wine, beer and spirits, and then combined to derive an overall amount of ethanol consumed. Follow-up was carried out by biennial mailed questionnaire and by consulting county death registrations. During 4.5 years of follow-up 126 incident cases of colorectal cancer occurred. The crude, age-adjusted RRs were 1.5 (95% CI, 1.0-2.4) and 1.9 (1.3-2.9) for those who drank 1-30 ml (0.8-24 g) ethanol/day and thos drinking more, respectively, compared with people who did not drink alcohol daily. After multivariable adjustment for smoking, relative weight and physical activity, the RR in men was 2.2 (95% CI, 1.2-3.8). The corresponding analysis for women showed no significant increase in risk. Another analysis of this study, omitting the 20 cases of rectal cancer, gave essentially the same results.

[The Working Group summarized of the results of the retrospective cohort studies of alcoholics and brewery workers, as follows: in eight studies that addressed stomach cancer, 234 cases were observed, with 251 expected; in nine that addressed cancer of the colon (including one on alcohol misusers), 251 cases were observed, with 245 expected; and in seven that addressed rectal cancer, 148 cases were observed, with 129 expected.]

(ii) *Case-control studies*

Stomach cancer (see Table 60): Wynder *et al.* (1963a) conducted a case-control study of stomach cancer and environmental variables, dietary factors, cigarette smoking and alcohol consumption in Iceland, Japan, Slovenia and the USA. A total of 367 male and 154 female cases, and 401 male and 252 female controls (without cancer) were included; all were hospital patients. No clear association was noted between risk for stomach cancer and type of alcohol consumed, although within the US component of the study, beer consumption was more prevalent in both male and female cases than in their controls. [The Working Group noted that, in the absence of quantitative consumption data and control for covariables, interpretation of the data is difficult.]

In a case-control study in New York State, USA, Graham *et al.* (1972) compared 160 men and 68 women with stomach cancer with 228 hospital controls individually matched to cases for sex, age, country of birth and family's ethnic background (as a proxy for socioeconomic status). All patients had originally been hospitalized in 1957-66 and had been interviewed routinely about social, behavioural and dietary traits by trained interviewers who were unaware of the patient's medical status. Usual frequency of consumption of beer, wine, gin, vodka and whisky was assessed, and an index of total alcohol consumption was derived. Comparison of the drinking profiles of cases and controls revealed no difference in overall alcohol intake. [The Working Group noted that it was not possible to estimate RR by level of consumption.]

Haenszel *et al.* (1972) carried out a case-control study of stomach cancer among Japanese in Hawaii. During 1963-69, 220 patients admitted to hospital with stomach cancer (135 men, 85 women) were enrolled for study; 96% of these cases were histologically confirmed. Two hospital controls were selected for each case, matched on sex, age, hospital and date of admission, excluding patients with stomach disorders and other alimentary tract cancers. Study subjects were interviewed about usual past frequency of intake of foods and alcoholic drinks. Saké and beer were the alcoholic drinks for which consumption differed most between cases and controls. The RR in beer drinkers compared with those who did not drink beer was 1.2; the RR for drinking saké was 1.4, confined substantially to those who drank it daily, for whom the RR was 2.2 ($p < 0.05$). [The Working Group noted that, since the data were analysed in a univariate fashion, covariables such as cigarette smoking and major nutrients could not be controlled for.]

Table 60. Summary of results of case-control studies of stomach cancer and alcohol consumption

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]	Comments
UK (Stocks, 1957)	Men (153, 4630)	Frequency of beer consumption	No association	
Iceland, Japan, Slovenia, USA (Wynder et al., 1963a)	Men (367, 401) Women (154, 252)	Frequency of alcohol consumption, by type of beverage	Few differences in consumption profile	No quantitative consumption data; no control of covariates
USA, Kansas City (Higginson, 1966)	Men (93, 279)	Open-ended interview about consumption of alcoholic beverages	No difference in overall alcohol consumption profile; prevalence of 'heavy periodical' drinking higher in cases	
USA, Buffalo (Graham et al., 1972)	Men (160, 160) Women (68, 68)	Frequency of consumption, by type of beverage	No difference in consumption profile	
Hawaii (Japanese) (Haenszel et al., 1972)	Men (135, 270) Women (85, 170)	Frequency of consumption, by type of beverage	Beer: Abstain 1.0 <6/month 1.2 [0.7-1.9] ≥6/month 1.2 [0.7-2.0] Saké: Abstain 1.0 <daily 1.0 [0.6-1.9] ≥daily 2.2 [1.1-4.4]	RR not controlled for dietary variables or social class
Norway (Bjelke, 1973)	Men, women (228, 1394)	Frequency of consumption, by type of beverage	No significant difference	RR for high versus low consumers among women gives positive association with beer
USA, Minnesota (Bjelke, 1973)	Men, women (83, 1657)	Frequency of consumption, by type of beverage	No significant difference	

Table 60 (contd)

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]	Comments
USA, Multicenter (Williams & Horm, 1977)	Men (120, 1668) Women (82, 3106)	Frequency and duration of consumption, by type of beverage	Men: no significant association; women: nonsignificant doubling in risk for wine and beer	Controlled for age, race, cigarette smoking
France (Hoey et al., 1981)	Men (40, 168)	Frequency of consumption, by type or amount	<80 g daily, 1.0 ≥80 g daily, 6.9 (3.3–14.3)	No adjustment for socio-economic status
France, Calvados (Tuyns et al., 1982)	Men, women (163, 1976)	Frequency of consumption, by type of beverage	Consumers versus nonconsumers: RR, 0.5 (95% CI, 0.2–1.8)	
Greece, Piraeus (Trichopoulos et al., 1985)	Men, women (110, 100)	Frequency and amount of consumption	Nonsignificant positive linear trend in risk Below median, 1.0 Above median, [1.4] [0.8–2.4]	RR calculated by Working Group
Poland, Cracow (Jedrychowski et al., 1986)	Men, women (110, 110)	Usual number of glasses per week, by type of beverage	RR in those drinking vodka before breakfast, 2.1 (1.0–4.2); no other difference	Adjusted for smoking, residence, diet

[a]Relative risk (RR) and 95% confidence interval ([] when calculated by the Working Group), when available

In a study in France (Hoey *et al.*, 1981), 40 newly diagnosed (1978-80) male cases of adenocarcinoma of the stomach were compared with 168 hospital controls. Cases and controls came from the same endoscopy unit, and controls were patients with cancer or polyp of the colon and rectum, hiatal hernia or gallstones. Three-quarters of the cases reported a current wine consumption of one or more litres per day (or an equivalent amount of alcohol from other beverages). The RR for those consuming more than 80 g ethanol daily compared with those consuming less was 6.9. Adjustment for tobacco use (for which an increased RR of 4.8 was found) did not substantially affect the RR observed for alcohol. The authors noted that, although high consumption of wine in France may be related to low social class (as is stomach cancer), social class was not adjusted for in their study.

A case-control study of stomach cancer was conducted by Trichopoulos *et al.* (1985) in Piraeus, Greece. Cases comprised 110 consecutive patients (57 men, 53 women) with histologically confirmed adenocarcinoma of the stomach admitted to two teaching hospitals during 1981-84. Controls comprised 100 orthopaedic patients hospitalized during the same period without cancers or other diseases of the digestive system. All subjects were interviewed by the same interviewer, who recorded the usual frequency of consumption of foods and alcohol before the onset of the present disease/disorder. There was no linear trend of increasing risk with increasing frequency of alcohol consumption. [The Working Group noted, however, that comparison of subjects with consumption above the median (value not given) with those with a consumption below the median yields a RR of 1.4.]

Jedrychowski *et al.* (1986) carried out a case-control study of stomach cancer in relation to diet and alcohol consumption in Cracow, Poland, in 1980-81. Each of an incident series of 110 histologically confirmed cases of adenocarcinoma of the stomach was individually matched by sex and age to a hospital patient without obvious gastrointestinal disease or dietary abnormality, who was interviewed in hospital. Alcohol consumption was recorded as usual number of glasses [volume unspecified] per week of beer, wine and vodka. After adjustment for smoking, residence and diet, the RR for stomach cancer associated with consumption of vodka before breakfast was 2.1, 33 cases reporting this habit; however, there was no overall difference between cases and controls with regard to consumption of beer, wine or spirits (vodka). The authors commented that the observed increase in risk associated with drinking vodka on an empty stomach was biologically plausible. [The Working Group noted that reliance on place of residence as an indicator of social class might have resulted in residual confounding.]

Large-bowel cancer (see Table 61): Wynder and Shigematsu (1967) conducted a case-control study of colorectal cancer, based in a New York hospital, in which 791 cancer cases were compared with two groups of controls matched for age and sex: cancer patients with cancers other than of the alimentary and respiratory tracts and patients with nonneoplastic diseases other than pulmonary arterial disease and chronic respiratory diseases. Information about the amount of alcohol consumed was obtained at interview for 492 cases and 273 controls. Among men, there was no difference in consumption for those with cancers at most subsites in the large bowel, with the exception of patients with rectal cancer in whom there was a significantly higher percentage of heavy drinkers than in the controls. There was no such difference between female cases and controls. There was a significantly higher

Table 61. Summary of results of case-control studies of large-bowel cancer and alcohol consumption

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]	Comments
UK (Stocks, 1957)	Colon and rectum: men (166, 4630)	Frequency of consumption	Beer <daily, 1.0 Beer ≥ daily, 1.4 (0.9-2.1)	RR adjusted for sex and age only, calculated by the Working Group
USA, Kansas City (Higginson, 1966)	Colon and rectum: men (340, 1020)	Open-ended questionnaire about consumption of alcoholic beverages	No difference in alcohol consumption	
USA, New York (Wynder & Shigematsu, 1967)	Colon: men (174, 206) women (114, 67) Rectum: men (140, 206) women (64, 67)	Frequency and pattern of drinking, by type of beverage	Rectal cancer significantly associated with heavy drinking; significantly more beer drinkers among male rectal and colon cancer cases than controls	No adjustment for social and other behavioural factors
Norway (Bjelke, 1973)	Colon: men, women (162, 1394) Rectum: men, women (116, 1394)	Frequency of consumption, by type of beverage	No difference observed	Matching ignored in analysis
USA, Minnesota (Bjelke, 1973)	Colon: men, women (259, 1657) Rectum: men, women (114, 1657)	Frequency of consumption, by type of beverage	Colon: significant positive association with consumption of spirits in men; significantly negative in women Rectum: significant positive association with beer consumption for men and women combined	Matching ignored in analysis
USA, Multicenter (Williams & Horm, 1977)	Colon: men (294, 1329) women (359, 2691) Rectum: men (165, 1329) women (138, 2691)	Frequency and duration of consumption, by type and amount	Colon (men): Total Wine Beer Spirits Abstainers 1.0 1.0 1.0 1.0 <50 oz-yr 1.4 1.1 1.2 1.5 ≥50 oz-yr 1.5* 2.1* 1.7* 1.6* Rectum: RR, 2.0* for high total alcohol intake in women	RR adjusted for age, race, cigarette smoking; *, significant
France, Calvados (Tuyns *et al.*, 1982)	Colon: men, women (142, 1976) Rectum: men, women (198, 1976)	Frequency of consumption, by type of beverage	Colon: 1.4 (0.3-5.7) Rectum: 1.6 (0.5-5.5)	Consumers *versus* abstainers

Table 61 (contd)

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]	Comments
Canada, Toronto (Miller, A.B. et al., 1983)	Colon: men, women (348, 542) Rectum: men, women (194, 335)	Frequency of consumption, by type and amount	No association with colon cancer Rectal cancer: M F Beer: Low 1.0 1.0 Medium 0.7 1.6 High 1.3 1.6	RR adjusted for education, diet, smoking
USA, New York (Kabat et al., 1986)	Rectum: men (130, 336) women (88, 249)	Frequency and duration of consumption, by type of beverage	No association with wine or spirits consumption Beer: M F Abstainers 1.0 1.0 Occasional 1.6 (0.9-2.8) 0.5 (0.3-1.0) 1-7.9 oz [24-190 g]/day 1.3 (0.7-2.4) 0.5 (0.2-1.2) 8-31.9 oz [192-766 g]/day 1.8 (0.9-3.5) 0.7 (0.1-3.2) ≥32 oz [≥768 g]/day 3.5 (1.8-7.0) –	RR, 2.7 (1.3-5.7) for men drinking ≥32 oz [≥768 g]/day, adjusted for religion and education
Australia, Adelaide (Potter & McMichael, 1986)	Colon: men, women (220, 438) Rectum: men, women (199, 396)	Frequency of consumption, by type and amount	Total alcohol: Increased risk (nonsignificant) for colon and rectal cancer in women Spirits: M F Colon cancer 1.0 2.0 Rectal cancer 1.0 1.5	Matched RR (≥12.9 g/day versus <0.01 g/day) calculated by Working Group
Australia, Melbourne (Kune et al., 1987a)	Colon and rectum: men, women (715, 727)	Estimated cumulative intake, by type of beverage	Colon: no significant association Rectum: Beer quartiles: M F 1 1.0 1.0 2 1.7* 1.6 3 1.8* 1.6 4 1.9* 2.1	RR adjusted for dietary variables RR changed little when also adjusted for other alcoholic beverages; *, significant

[a]Relative risk (RR); 95% confidence intervals in parentheses

proportion of beer drinkers among male cases of rectal and colon cancer (35% and 31%, respectively), compared with 19% of controls, but there was no difference in other types of alcohol consumed. The authors conclude that 'the excess of heavy drinkers, particularly of beer, among men with rectal cancer appeared to reflect factors such as religious differences, smoking habits and the lower socioeconomic status of that group'. There was no difference in alcohol consumption between the rectal cancer group and the second control group.

Miller, A.B. *et al.* (1983) conducted a case-control study in Toronto, Canada, of 348 patients with colon cancer and 194 with rectal cancer, compared with two series of controls consisting of 542 individually matched neighbourhood and 535 frequency matched hospital controls. Standardized interview information was obtained on usual frequency of food and alcohol consumption. Analysis was done for groups of foods rather than nutrients, and these included alcoholic beverages, in particular beer. There was some evidence of an increased risk for rectal cancer, but not colon cancer, in association with beer intake; nonsignificantly elevated RRs of 1.3 for men and 1.6 for women were found among individuals in the highest consumption tertile. There was no indication of an association between colon or rectal cancer and other types of alcohol consumption.

The association between beer drinking and cancer of the rectum was investigated by Kabat *et al.* (1986) in a case-control study of 130 male and 88 female rectal cancer cases, all histologically confirmed, and 336 males and 249 female controls. The controls consisted of patients with cancers other than of the digestive tract and disease conditions not associated with tobacco use. A maximum of three controls was matched to each case on the basis of age, sex and calendar year of hospital interview. Information on consumption of beer, wine and spirits throughout adulthood (quantity and duration), and on smoking and socio-demographic characteristics was obtained by standardized interview. Beer intake was significantly associated with estimated risk of rectal cancer in men, the RR increasing with consumption. For drinkers of 32 oz or more of beer per day, the RR was 3.5. There was no association with duration of beer drinking. A nonsignificant inverse association with consumption was seen for women; however, only nine cases and 40 controls drank beer more than occasionally. In conditional multiple logistic regression analyses, the RR for beer drinking decreased slightly when controlled for potential confounding variables, and the RR for men drinking ≥32 oz/day, when adjusted for religion and education, was 2.7. Consumption of wine or spirits showed no association with rectal cancer.

Potter and McMichael (1986) reported a population-based case-control study of 419 incident cases of large-bowel cancer (220 colon, 199 rectum) and 732 community controls, interviewed regarding diet and alcohol in 1979-81 in Adelaide, Australia. Information regarding food and alcohol intake was obtained using a quantitative frequency questionnaire; the reproducibility of information about alcohol consumption was documented in a study of a subgroup of the study population re-interviewed by that research group in Adelaide (Rohan & Potter, 1984). Analysis by quintile of alcohol consumption showed that total alcohol intake was associated with nonsignificantly increased risks of both colon and rectal cancer in women but not in men. In both men and women, there were increased risks for colon and rectal cancer associated with consumption of spirits. For colon cancer, there was a statistically significant, approximate doubling of risk associated with drinking a glass [volume unspecified] of spirits per day in women, and with drinking two glasses per day in men, relative to abstainers. For rectal cancer, there was a weaker association with consumption of spirits. There was no association between beer consumption and cancer at either site.

As part of a large investigation of colorectal cancer incidence, etiology and survival in Melbourne, Australia, a case-control study was conducted to identify whether diet and alcohol, among other variables, were associated with colorectal cancer (Kune *et al.*, 1987a). The authors compared 715 incident cases of adenocarcinoma of the large bowel with 727 age- and sex-matched community controls. Information about the total lifetime intake of specific alcoholic beverages was obtained by interview, and data were classified by level of consumption of beer, wine, spirits and total alcohol. There was little evidence of an association of any of the alcohol variables with the risk of colon cancer; however, beer was found to be a significant risk factor for rectal cancer in men (RR, 1.0, 1.7, 1.8, 1.9 for four increasing quartiles of consumption), controlling for ten dietary variables and for other categories of alcoholic beverage. This effect was greatest in older men. RRs were similar in women but did not attain significance. Consumption of spirits was associated with a reduced risk of rectal cancer in men. [The Working Group noted that some controls were re-interviewed (Kune *et al.*, 1987b), which seriously limits the interpretation of these findings.]

Stomach and colorectal cancer (see Tables 60 and 61): In an early case-control study by Stocks (1957) in North Wales and Liverpool, UK, trained interviewers obtained histories from hospitalized patients with and without cancer. Within each residential area, the frequency of consumption of alcohol by cancer patients aged 45-74 years was compared with that expected on the basis of sex- and age-specific frequency distributions of the non-cancer patients, who totalled 4630 men and 4900 women 45-74 years old. In men, usable data were available from 153 stomach cancer patients and 166 patients with colorectal cancer; beer drinking was positively associated with intestinal cancer (RR calculated by the Working Group to be 1.4 in those who drank daily or weekly in comparison with those who drank less often) but not with stomach cancer. [The Working Group noted that, because of the very low prevalence of self-reported alcohol consumption in women, no informative comparison could be made.]

A case-control study of 93 male cases of stomach cancer and 279 controls, and of 340 male cases of colorectal cancer and 1020 controls was conducted by Higginson (1966). Cases were patients admitted to seven hospitals in Kansas City, USA, with histologically confirmed cancer; controls were hospital patients with no obvious gastrointestinal disease or recent dietary abnormality, frequency matched with cases for sex, age and race. Alcohol consumption was estimated from interviews conducted in hospital. For both stomach and colorectal cancers, the alcohol consumption profiles of cases and controls were virtually identical. Stomach cancer was associated with 'heavy periodical' (i.e., weekend) drinking, but the numbers involved were small (five cases and three controls).

In Norway, Bjelke (1973) compared 228 stomach cancer cases (147 male, 81 female), 162 colon cancer cases (89 male, 73 female), 116 rectal cancer cases (64 male, 52 female) and 221 unconfirmed cases, with 1394 hospital controls matched for sex, age, hospital and interviewer. Consumption of beer, wine and spirits and other dietary items was assessed by interview in terms of six categories of usual frequency. The prevalence of use of any kind of beverage and the mean frequencies were very similar among cases and controls for cancer at each of the sites, in both men and women. In women, stomach cancer was positively associated with beer consumption, but negatively associated with consumption of spirits. [The Working Group noted that each case series was compared with the whole series of controls without taking the original matching into account.]

In a case-control study carried out in Minnesota, USA, the design of which was very similar to his Norwegian study, Bjelke (1973) compared 83 stomach cancer cases (67 male, 16 female), 259 colon cancer cases (144 male, 115 female) and 144 rectal cancer cases (74 male, 40 female) aged 39-75 years, with 1657 hospital controls matched for age, sex, race and hospital, excluding persons with gastrointestinal diseases and a few other specified conditions. A significant positive association was seen for men and women combined for rectal cancer and beer consumption. For colon cancer and consumption of spirits, the association was significantly positive for men and negative for women.

In a patient interview study (Williams & Horm, 1977) as part of the Third National Cancer Survey (see description, pp. 170-171), 202 stomach cancer cases (120 male, 82 female), 653 colon cancer cases (294 male, 359 female) and 303 rectal cancer cases (165 male, 138 female) were compared with 1209 male and 2609 female controls, who were other cancer cases in the survey. After controlling for age, race and cigarette smoking, the risk for colon cancer among men was significantly increased with high total ethanol consumption (RR, 1.5) and for drinking beer, wine or spirits. The risk for neither rectal nor stomach cancer showed a clear association with alcohol consumption in men. Among women, the risk for rectal cancer was significantly increased (RR, 2.0) with high consumption of total ethanol, while the risks for colon and stomach cancers showed no statistically significant increase. There was a moderate association between stomach cancer in women and consumption of wine and beer (but not spirits).

Tuyns *et al.* (1982) conducted a population-based case-control study in which 163 stomach cancer cases, 142 colon cancer cases and 198 rectal cancer cases were identified and interviewed prospectively, during 1975-80, in Calvados, France. A total of 1976 population controls were interviewed during 1973-80, comprising a random sample of all people aged over 20 years in the source population. A standard interview questionnaire was used, which was developed for French patterns of alcohol consumption and administered by specially trained dieticians. There were nonsignificantly increased RRs for colon cancer (1.4; 95% CI, 0.3-5.7) and rectal cancer (1.6; 0.5-5.5) in alcohol consumers *versus* abstainers, and a nonsignificantly decreased RR for stomach cancer (0.5; 0.2-1.8).

(*f*) *Cancer of the liver*

(i) *Cohort studies* (descriptions of studies of cancers at many sites are given on pp. 158-164)

In most of the cohort studies on liver cancer, summarized in Table 62, it is probable that several cases classified as having primary liver cancer in fact had metastatic liver cancer,

Table 62. Relative risks for liver cancer in cohort studies

Study and reference	No. of subjects	Relative risk[a]	Comments
Norwegian Alcoholics (Sundby, 1967)	6 deaths	2	Compared with Norwegian population
Finnish			
Alcohol Misusers	66 cases	1.5*	
Alcoholics (Hakulinen et al., 1974)	2 cases	2.5	
Massachussetts Alcoholics (Monson & Lyon, 1975)	4 deaths	1	
UK Alcoholics (Adelstein & White, 1976)	5 deaths	5.8* in males	
Dublin Brewery Workers (Dean et al., 1979)	7 deaths	1.3	
US Veterans Alcoholics (Robinette et al., 1979)	2 deaths	>1	
Danish Brewery Workers (Jensen, 1980)	29 cases	1.5*	
Canadian Alcoholics (Schmidt & Popham, 1981)	4 deaths	2	
Japanese Prospective Study (Hirayama, 1981)	-	1.3* nonsmokers, 0.9 <200 000 cig., 1.3 200 000-400 000 cig., 1.2 >400 000 cig., 1.5	Daily drinkers; RRs calculated by the Working Group
Japanese Doctors (Kono et al., 1986)	51 deaths	ex-drinkers, 1.4 (0.4-4.8) occasional drinkers, 1.5 (0.6-3.8) daily drinkers <2 *go*, 2.0 (0.8-5.1) daily drinkers >2 *go*, 2.7 (1.0-6.8)	RR adjusted for age and smoking
Japan (Shibata et al., 1986)	21 deaths	7.5* for *shochu* drinkers	Fishing area - RR not adjusted for smoking

[a]*, significant; ;95% confidence interval in parentheses

because of difficulties in diagnosis. Furthermore, it is clear that, in some of these studies, cases of primary liver cancer were grouped with other cancers. Both practices would tend to affect (probably underestimate) the strength of the association between alcohol consumption and risk for primary liver cancer.

In the prospective Japanese study (Hirayama, 1975, 1978, 1981), the most recent (Hirayama, 1981) age-adjusted rate ratio for primary liver cancer between daily drinkers and nondrinkers was calculated by the Working Group to be 1.3, which is significantly different from the null value of 1.0. [The Working Group noted that data on hepatitis B virus serology were not available.]

In the study of Japanese doctors (Kono *et al.*, 1983, 1985, 1986), the numbers of deaths (and age-adjusted death rates per 10 000 per year) are given for primary liver cancer (ICD-8 155, 197.8) as follows: seven deaths (3.6) among nondrinkers, four (4.9) among ex-drinkers, 14 (5.7) among occasional drinkers, 13 (7.1) among daily drinkers of less than 2 *go* (1 *go* = 180 ml saké = 22 g ethanol) and 13 (9.0) among daily drinkers of more than 2 *go*. Excluding ex-drinkers, and using logistic regression to control for age and tobacco smoking, the partial regression coefficient for alcohol intake is 0.317 (standard error, 0.125). The Working Group calculated that this corresponds to a statistically significant RR for primary liver cancer of 1.4 for an increase in alcohol consumption of 1 *go* per day. In categorical assessments, the RR (and 95% CI) for primary liver cancer, with nondrinkers as referents, were 1.4 (0.4-4.8) for ex-drinkers, 1.5 (0.6-3.8) for occasional drinkers, 2.0 (0.8-5.1) for daily drinkers of less than 2 *go*, and 2.7 (1.0-6.8) for daily drinkers of more than 2 *go*. [The Working Group noted that data on hepatitis B virus serology are not available, and that no information is given about the actual proportion of cases with primary liver cancer in the rubric 197.8, unspecified liver cancer.]

In the study of Hawaiian Japanese (Blackwelder *et al.*, 1980), seven deaths were due to primary liver cancer and 16 to cirrhosis of the liver. The mean ethanol consumption in the seven individuals with primary liver cancer had been 12.0 ml [9.5 g]/day, compared to 36.8 ml [29 g]/day among individuals who had died from cirrhosis of the liver, and to 13.6 ml [11 g]/day in living members of the cohort. All values were ascertained at the initial baseline examination and were not age-standardized.

Another cohort study in which role of alcohol and tobacco in the etiology of primary liver cancer was explored in the general Japanese population was recently reported (Shibata *et al.*, 1986). The study was based on follow-up of 639 men in a farming area and 677 men in a fishing area, in the context of a longitudinal study to evaluate risk factors for coronary heart disease. There was no effect of saké drinking in either the farming or the fishing area nor any effect of drinking *shochu* (a distilled alcoholic beverage made in Japan, containing about 25% alcohol) in the farming area. However, in the fishing area, the observed (18) to expected (2.4) ratio among *shochu* drinkers was 7.5 ($p < 0.001$), with an apparent but nonsignificant dose-trend. [The Working Group noted that the association is not confounded by tobacco smoking, but the lack of data concerning hepatitis B virus, the absence of a similar association with *shochu* in the other study area, and the small overall study size make interpretation of these findings difficult.]

In several studies of cohorts of persons with high alcohol intake, the observed number of deaths from primary liver cancer has been compared with the number expected on the basis of the age-, sex- and calendar-time-specific mortality from this cancer in a reference population. In the study of Norwegian alcoholics (Sundby, 1967), six deaths were observed, with 3.1 expected in Norway. In the Canadian study of Schmidt and de Lint (1972) on alcoholics, no death from primary liver cancer was observed. [The Working Group estimated that approximately two would have been expected on the basis of expected figures in studies of similar size and background rates.] In this study, a high excess of deaths due to cirrhosis of the liver was observed (56 among men and 12 among women, with 4.9 and 0.5 expected), but the authors of the study consider it unlikely that deaths due to primary liver cancer had been misdiagnosed as due to cirrhosis, since most deaths occurred in large hospitals and autopsies were performed on 55% of those who died from cirrhosis.

In a five-year mortality study in one company in the USA of 922 alcoholics and an equal number of nonalcoholics, individually matched by age, sex, payroll, class and geographic location, no death from primary liver cancer was observed (Pell & D'Alonzo, 1973). [The Working Group estimated that approximately one would have been expected.] An excess of deaths due to cirrhosis of the liver was found among alcoholics (11 deaths due to cirrhosis, compared to none among nonalcoholics).

In the study of UK alcoholics (Nicholls *et al.*, 1974; Adelstein & White, 1976), there were five deaths from liver cancer (including extrahepatic bile ducts) among men, while 0.9 would have been expected, giving a significant SMR of 5.8. In the study of Finnish alcohol misusers and alcoholics (Hakulinen *et al.*, 1974), there were 66 cases of primary liver cancer in the misusers cohort and two in the alcoholics cohort, with 44.3 and 0.8 expected, respectively; the first comparison gave a significant result. In the study of Massachussets alcoholics, Monson and Lyon (1975) found four deaths from primary liver cancer (including biliary passages), with 4.2 expected. In the cohort study of male Dublin brewery workers (Dean *et al.*, 1979), there were seven deaths from primary liver cancer with 5.5 expected from Dublin death rates. In the cohort study of male Danish brewery workers (Jensen, 1980), there were 29 incident cases of primary liver cancer with 19.2 expected; this result was significant. In the study of alcoholic US veterans (Robinette *et al.*, 1979), there were two deaths in a category that included primary liver cancer (as well as other rare cancers in ICD-8 rubrics 152, 156, 158 and 159), whereas no such death was observed in a comparison age-matched group. In the cohort study of male alcoholics in Canada (Schmidt & Popham, 1981), four deaths from primary liver cancer (ICD-8, 155, 156) were observed with 2.0 expected.

[The Working Group noted that, taken together, the results of these ten cohort studies on alcoholics generate 125 observed cases of liver cancer *versus* 83.3 expected. The ratio, based on the three most reliable studies, is 1.5 (1.2-1.9). The ratio based on the total numbers of observed and expected cases in all the cohorts is 1.5 (1.3-1.8). Both are significant at the 1% level.]

(ii) *Case control studies*

The results of case-control studies of primary liver cancer are summarized in Table 63.

Table 63. Summary of results of case-control studies of primary liver cancer and alcohol consumption

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]
France, Paris (Schwartz et al., 1962)	Men (61, 61)	Average daily ethanol intake	High but equal ethanol consumption among cases and controls
USA, Multicenter (Williams & Horm, 1977)	Men (18, 1770) Women (10, 3178)	Three categories of wine, beer, spirits or total	Suggestive positive but not significant association Men / Women Nondrinkers 1.0 / 1.0 Moderate drinkers 0.5 / 5.1 Heavier drinkers 2.8 / –
Switzerland, Geneva (Infante et al., 1980b)	Men (31, 207) Women (4, 226)	Main daily and life-long ethanol consumption	Ethanol consumption among cases twice as high as that among controls
Philippines (Bulatao-Jayme et al., 1982)	Men (74, 74) Women (16, 16)	Categorization into 'heavy' (38.4 g) and 'light' (9.8 g) drinkers using mean ethanol intake per day of all subjects	Light aflatoxin, light alcohol: 1.0 Light aflatoxin, heavy alcohol: 3.9* Heavy aflatoxin, light alcohol: 17.5* Heavy aflatoxin, heavy alcohol: 35.0*
Hong Kong (Lam et al., 1982)	Men (95, 95) Women (12, 12)	'Alcohol consumption', details not given	No significant positive association
USA, New Jersey (Stemhagen et al., 1983)	Men (178, 356) Women (87, 174)	Categorization into nondrinker, light, moderate, medium-heavy and heavy drinker	In both sexes, statistically significant linear trends with increasing ethanol consumption Men / Women Nondrinkers 1.0 / 1.0 Light 1.0 (0.5–2.1) / 1.7 (0.7–4.2) Moderate 1.2 (0.5–2.7) / 2.2 (0.9–5.7) Medium 2.5 (1.0–6.5) / 3.7 (0.2–93.6) Heavy 2.0 (0.8–5.1) / 5.6 (0.8–38.6)

Table 63 (contd)

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]
USA, Los Angeles County (Yu *et al*., 1983)	Men (50, 50) Women (28, 28)	Three categories of ethanol intake: low, moderate, high	0–9 g/day, 1.0 10–79 g/day, 0.9 (0.4–1.9) ≥80 g/day, 4.2 (1.3–13.8)
Sweden (Hardell *et al*., 1984)	Hepatocellular carcinoma: men (83, 166) Cholangiocarcinoma: men (15, 30)	Categorization into nondrinkers, light consumers of spirits (≤4 bottles/year), moderate consumers (>1 bottle/month–<1 bottle/week), heavy consumers (>1 bottle/week) (1 bottle = 370 ml spirits)	Alcohol: 0–79 g/day / ≥80 g/day Non-/ex-smokers: 1.0 / – ≤1 pack/day: 1.4 (0.6–3.4) / 0.8 (0.1–4.6) >1 pack/day: 1.8 (0.7–5.0) / 14.0 (1.7–113.9) Nondrinkers, 1.0 Light drinkers, 2.1 (0.9–5.1) Moderate drinkers, 2.9 (1.0–8.7) Heavy drinkers, 4.3 (1.8–10.8)
USA, five states (Austin *et al*., 1986)	Men (60, 110) Women (26, 51)	Categorization into no use, infrequent use, occasional use, regular use (at least once/day)	Statistically significant dose-dependent association with frequency of alcohol intake Nondrinkers 1.0 Infrequent drinkers 1.4 Occasional drinkers 2.3 Regular drinkers 2.6
Greece, Athens (Trichopoulos *et al*., 1987)	Men (173, 400)	Total daily ethanol consumption in grams	No association for ethanol consumption with or without underlying cirrhosis; for liver cancer with cirrhosis, 'heavy' ethanol consumption (>70 g/day), adjusted RR, 1.2

[a]Relative risk; 95% confidence intervals in parentheses; *, significant

In a large case-control study of all cancers in Paris, Schwartz *et al.* (1957, 1962; see description, p. 167) grouped 61 male cases of primary liver cancer, pancreatic cancer and cancers of the peritoneum, and compared them with matched hospital controls. The proportion of alcoholics and the mean alcohol intake were almost identical in the two groups.

In a study conducted within the Third National Cancer Survey (Williams & Horm, 1977; see description, pp. 170-171), there were 18 cases of primary liver cancer in men and ten among women. Men in the higher time-weighted alcohol consumption category had a RR for primary liver cancer of 2.8, after adjustment for smoking, but there was no elevation of risk among men in the moderate consumption category (RR, 0.5). There were no women in the higher alcohol consumption category; among those in the moderate consumption category, the tobacco-adjusted RR for primary liver cancer was 5.1. None of these associations was significant.

In a case-control study in Geneva, with 31 male and four female cases of histologically confirmed primary liver cancer and 207 and 226 population controls (among whom the participation rate was 70%), Infante *et al.* (1980a,b) found substantially higher age-standardized alcohol consumption among the cases than among the controls (47 g ethanol in men; 12 g in women). The differences in alcohol consumption were not related to the small differences in tobacco smoking between cases and controls. Alcohol consumption was not higher among primary liver cancer cases with cirrhosis (72 g in men, 23 g in women) than among those without cirrhosis (101 g in men). [The Working Group noted that information concerning hepatitis B virus serology was not available.]

In a case-control study of 90 histologically confirmed cases of primary liver cancer (74 male, 16 female) and 90 age- and sex-matched hospital controls with normal liver function tests in the Philippines, Bulatao-Jayme *et al.* (1982) investigated the role of alcohol and aflatoxin intake in the etiology of primary liver cancer. Intake of alcohol and of aflatoxin (see IARC, 1976b, 1987a) were ascertained using dietary questionnaires and on the basis of aflatoxin contamination of various foods and the ethanol content of alcoholic beverages. In comparison with 'light aflatoxin-light alcohol' consumers (referent group), the RRs were 3.9 among 'light aflatoxin-heavy alcohol' consumers, 17.5 among 'heavy aflatoxin-light alcohol' consumers and 35.0 among 'heavy aflatoxin-heavy alcohol' consumers. [The Working Group noted that the lack of data concerning hepatitis B virus serology in this study, and the probable correlation between prevalence of hepatitis B surface antigen carrier state and both alcohol and aflatoxin intake hinder interpretation of the results.]

In a study of 107 cases (95 male, 12 female; 106 histologically confirmed) and 107 controls matched for sex, age and hospital in Hong Kong, Lam *et al.* (1982) found that serum hepatitis B surface antigen carrier state and tobacco smoking were independent risk factors for primary hepatocellular carcinoma. While no data were reported, the authors stated that neither alcohol intake nor aflatoxin contamination of foods was significantly related.

Stemhagen *et al.* (1983) studied 265 cases (178 male, 87 female) of histologically confirmed primary liver cancer (216 hepatocellular carcinoma) and 530 controls (356 male, 174 female) matched for age, sex and county of residence in New Jersey, USA, by interviews mostly (96%) with next-of-kin; dead cases were matched through death certificates wi.. dead controls. There were statistically significant linear trends with increasing alcoho consumption up to RRs of 2.0 and 5.6 among heavily drinking men and wom respectively. Drinking habits were also studied by type of alcohol consumed, but th numbers were small, and the only remarkable finding was a strong association amon women between exclusive beer drinking (RR, 10.6; 95% CI, 2.6-42.9) and primary li cancer. No association was found between primary liver cancer and tobacco smoking probably because most of the controls had tobacco-related diseases, notably ischae heart disease. [The Working Group noted that data concerning hepatitis B virus serolo were not available.]

Yu *et al.* (1983) studied 78 cases (50 male, 28 female) of hepatocellular cancer identif through the Los Angeles County Cancer Surveillance Program and 78 age-, sex- and race-matched neighbourhood controls in California, USA, and found a statistically significant association with high ethanol consumption: the RR (and 95% CI) for intake 10-79 g/day was 0.9 (0.4-1.9) and that for ≥80 g/day was 4.2 (1.3-13.8). [The Working Group noted that information concerning hepatitis B virus serology was not available.]

In a study in Sweden (Hardell *et al.*, 1984), 83 male deaths from histologically confirmed hepatocellular carcinoma and 15 from histologically confirmed intrahepatic cholangio-cellular carcinoma, identified through the Swedish Cancer Registry, were each match with two deceased population controls drawn from the National Population Register; relatives were asked to complete written questionnaires. A statistically significant, dose-dependent association of consumption of spirits was found with hepatocellular carcinoma and a suggestive association with intrahepatic cholangiocarcinoma. Only 34% of the hepatocellular carcinoma cases were reported to have cirrhosis. [The Working Group not that data on hepatitis B virus serology were not available.]

In a study in five states in the USA on 86 cases (60 male, 26 female) of hepatocellular carcinoma (80 histologically confirmed), diagnosed in any of 12 hospitals, and 161 (1 male, 51 female) age-, sex- and race-matched controls, excluding those with tobacco-related diseases and primary liver diseases, Austin *et al.* (1986) found that chronic hepatitis B virus infection was strongly related to hepatocellular carcinoma and that there was also moderately strong, dose-dependent association between alcohol consumption and risk for liver cancer, adjusted for age and hepatitis B virus status.

Trichopoulos *et al.* (1987) studied 194 cases (173 male, 21 female) of hepatocellular carcinoma (113 histologically confirmed) admitted to three major hospitals in Athens, Greece, and 456 (400 male, 56 female) hospital controls with diagnoses other than cancer or liver disease. A strong, highly significant association was seen between hepatocellular carcinoma and both serum hepatitis B surface antigen carrier status and tobacco consumption, but there was no association (with or without underlying cirrhosis which was in most cases, hepatitis B virus-related) with ethanol consumption after adjustment for age, sex, carrier status and tobacco smoking.

(iii) *Studies of joint exposure*

Hirayama (1981) found an interaction between tobacco smoking and alcohol drinking in the causation of primary liver cancer. The rate ratios, calculated by the Working Group, between daily drinkers and other males were 0.9 among nonsmokers, 1.3 among cumulative smokers of up to 200 000 cigarettes, 1.2 among cumulative smokers of 200 000-400 000 cigarettes, and 1.5 among cumulative smokers of more than 400 000 cigarettes. [The Working Group noted that details which would allow alternative statistical calculations to be made are not given.] Yu *et al.* (1983) found a stronger association with alcohol drinking among heavy cigarette smokers than among those who smoked less. Heavy smokers (>1 pack/day) who were also heavy drinkers (>80 g ethanol/day) had a RR of 14.0 (1.7-113.9), while the RR for all heavy drinkers was 4.2. Austin *et al.* (1986) found no interactive effect of tobacco and alcohol consumption and risk for hepatocellular carcinoma.

Interactive effects between ethanol and hepatitis B virus in the causation of primary liver cancer have been postulated by several authors on the basis of relatively small or inadequately controlled clinical, pathological or clinicopathological studies. Support for this notion was recently provided by a case-control study (Oshima *et al.*, 1984) on liver cancer, performed within a cohort of 8646 male voluntary blood donors who were found to be hepatitis B surface antigen-positive during examination at the Red Cross Blood Center in Osaka, Japan, during the period 1972-75 and were followed through 31 December 1980, for an average period of 6.2 years. Twenty cases of primary liver cancer were found (3.03 expected; RR, 6.6). For these 20 cases of liver cancer and 40 age-matched controls selected from healthy hepatitis B virus carriers, detailed information on tobacco smoking and alcohol drinking was obtained. Drinking habits were classified into three categories: heavy (not less than 3 *go* of saké or other alcoholic beverages, equivalent to 80 ml [63 g] ethanol/day), moderate and none or light (less than 1 *go* of saké or the equivalent of 27 ml [21 g] ethanol/day). A strong, dose-dependent, significant, positive association (RR, up to 8.0; 95% CI, 1.3-49.5) between alcohol drinking and primary liver cancer was observed, which was apparently not confounded by tobacco smoking (also positively related to the occurrence of primary liver cancer).

Possible interactions between ethanol and aflatoxins in the etiology of liver cancer have been investigated in two studies; a more than additive effect was reported by Bulatao-Jayme *et al.* (1982), whereas no effect of either ethanol or aflatoxin was found by Lam *et al.* (1982).

(*g*) *Cancer of the pancreas*

(i) *Cohort studies* (descriptions of studies of cancer at many sites are given on pp. 158-164)

In none of the nine cohorts with high alcohol intake (see Table 64) was there a significantly elevated number of pancreatic cancers (Sundby, 1967; Schmidt & de Lint, 1972; Hakulinen *et al.*, 1974; Adelstein & White, 1976; Dean *et al.*, 1979; Monson & Lyon, 1979; Robinette *et al.*, 1979; Jensen, 1980; Schmidt & Popham, 1981). In only four studies was the observed number of cases greater than five: seven in a follow-up of the study of Adelstein and White (1976; Nicholls *et al.*, 1974), 17 in the study of Dean *et al.* (1979), 44 in the study of Jensen (1980) and 11 in that of Schmidt and Popham (1981).

Table 64. Relative risks (RR) for pancreatic cancer in cohort studies

Study and reference	No. of subjects	RR	Comments
Norwegian Alcoholics (Sundby, 1967)	5 deaths	1.6	Compared with Norwegian population
		0.9	Compared with Oslo population
Canadian Alcoholics (Schmidt & de Lint, 1972)	1 death		
Finnish Alcoholics (Hakulinen *et al.*, 1974)	4 cases	1.8	
Massachusetts Alcoholics (Monson & Lyon, 1975)	3 deaths	0.6	
UK Alcoholics (Adelstein & White, 1976)	7 deaths	1.5	
Dublin Brewery Workers (Dean *et al.*, 1979)	17 deaths	1.2	Compared with Dublin population
		1.5	Compared with Irish population
US Veterans Alcoholics (Robinette *et al.*, 1979)	4 deaths	0.9	
Danish Brewery Workers (Jensen, 1980)	44 cases	1.1	
Canadian Alcoholics (Schmidt & Popham, 1981)	11 deaths	1.2	Compared with Ontario population
		1.1	Compared with US veterans
		0.8	Compared with US veterans with similar smoking habits

In the Japanese prospective study, the SMR for pancreatic cancer among men who consumed alcoholic beverages daily compared with those who did not was 1.1 after eight years (Hirayama, 1975), 0.9 after nine years (Hirayama, 1978) and 0.8 after 16 years (Hirayama, 1985). Furthermore, there was no evidence for an interaction between alcohol intake and tobacco smoking in the causation of pancreatic cancer (Hirayama, 1979).

In the Kaiser-Permanente study (Klatsky *et al.*, 1981), the numbers of pancreatic cancer deaths (and ten-year cumulated mortality per 1000 persons) were two (1.0) among nondrinkers, five (2.5) among light drinkers (two or fewer drinks/day); three (1.5) among moderate drinkers (three to five drinks/day); and six (3.0) among heavy drinkers (six or more drinks/day). The association appears to be positive but it is not statistically significant and does not show a clear dose-dependent pattern. Although subjects were matched for smoking habits, some residual confounding by duration and intensity of smoking could not be excluded.

Heuch *et al.* (1983) reported a cohort of 16 713 subjects, comprising a random sample of Norwegian males (48%), brothers of Norwegians who had emigrated to the USA (20%), and spouses and siblings (males and females) of individuals interviewed in a case-control study of gastrointestinal cancer (32%). For only 4995 men was information on both alcohol drinking and tobacco smoking or chewing available; among these, 18 histologically verified cases of pancreatic cancer occurred. Among 'frequent current users' of alcohol (drinking of beer or spirits at least 14 times per month), five histologically verified cases of cancer of the pancreas were observed, whereas the tobacco-adjusted expected number was 1.7. Among nondrinkers, the observed and expected numbers were three and 7.6, whereas in the intermediate category of moderate alcohol drinkers the corresponding figures were ten and 8.7. The authors interpreted their findings as strongly supportive of a causal role for alcohol ($p = 0.001$ for trend). [However, the authors' estimate of a RR of 10.8 between frequent and nonusers, which the Working Group was unable to reproduce, is based on only 18 cases and has a lower 95% confidence limit of 2.2 (Velema *et al.*, 1986). The Working Group noted that this fact, together with the apparent high nonparticipation rate of heavy drinkers during the formative phase of the cohort, and the conflicting evidence derived from histologically confirmed and nonconfirmed pancreatic cancer cases (among the latter, the association with alcohol intake appears to be negative), make a causal interpretation of the findings difficult.]

In the study of Japanese doctors (Kono *et al.*, 1983, 1986), deaths (and age-adjusted death rates) from pancreatic cancer (per 10 000 persons per year) were three (1.7) among nondrinkers, two (2.4) among ex-drinkers, five (2.1) among occasional drinkers, one (0.5) among daily drinkers of less than 2 *go* and three (2.4) among daily drinkers of more than 2 *go*. Excluding ex-drinkers, and using logistic regression to control for age and smoking, gives a partial regression coefficient for alcohol intake corresponding to a SMR of 1.0, implying that alcohol drinking does not increase the risk for pancreatic cancer.

In the study of Hawaiian Japanese (Blackwelder *et al.*, 1980), 13 deaths from pancreatic cancer were identified within eight years of the initial examination. The mean ethanol consumption in these 13 individuals was 13.7 ml (11 g)/day compared to 13.6 ml (11 g)/day in living members of the cohort.

Furthermore, in the five-year mortality study of 922 alcoholics and an equal number of nonalcoholics, individually matched by age, sex, payroll, class and geographical location in a US company, there were two deaths from pancreatic cancer among alcoholics and none among nonalcoholics (Pell & D'Alonzo, 1973).

[The Working Group noted that the observed number of deaths due to pancreatic cancer in all the cohort studies on alcoholics combined was 98, with ~ 84.4 expected. The pooled SMR (and 95% CI) is thus 1.2 (0.9-1.4).]

(ii) *Case-control studies*

The results of case-control studies of pancreatic cancer are summarized in Table 65.

Table 65. Summary of results of case-control studies of pancreatic cancer and alcohol intake

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]
Japan (Ishii *et al*., 1968, 1973)	Men, women (475, 122 261)	Categories of alcohol intake	RR, ~1.5 for drinkers *versus* nondrinkers
USA, three cities (Wynder *et al*., 1973a)	Men (100, 200) Women (42, 107)	Categorization into nondrinkers, occasional drinkers, regular drinkers	RR [1.3 (0.8–2.0)] for drinkers *versus* nondrinkers
USA, Multicenter (Williams & Horm, 1977)	Men (901, 1770) Women (85, 3178)	Three categories of wine, beer, spirits and total alcohol	RR (heavier *versus* nondrinkers) men, 1.3 women, 0.6
Switzerland, Geneva (Raymond *et al*., 1987)	Men, women (88, 336)	Mean weekly consumption of red wine and beer	90% CI red wine <1270 ml/week 1.0 (0.5–1.9) ≥1270 ml/week 0.9 (0.4–1.7) beer ≤900 ml/week 0.7 (0.3–1.3) ≥900 ml/week 2.9 (1.3–6.3)
USA (Lin & Kessler, 1981)	Men (57, 57) Women (37, 37)	No clear definition	Patients drank more wine than controls (16.5% *versus* 8.3%), $p < 0.05$ for ≥2 glasses/day
USA, Boston and Rhode Island (MacMahon *et al*., 1981)	Men (218, 307) Women (149, 337)	Categorization into nondrinkers, occasional drinkers, regular drinkers	Men / Women nondrinkers 1.0 / 1.0 occasional 1.3 (0.7–2.6) / 0.8 (0.5–1.3) regular 1.3 (0.6–2.6) / 0.5 (0.3–1.1)
Greece, Athens (Manousos *et al*., 1981)	Men (32, 172) Women (18, 34)	Regular drinkers of >10 g ethanol daily	RR 0.7 (0.3–1.3) for regular drinkers *versus* others
USA, California (Haines *et al*., 1982)	Men (56, 112) Women (60, 120)	Categorization into alcohol intake < once a day, regular daily consumption, patients with alcohol-related problems	No association

Table 65 (contd)

Place (reference)	Subjects (cases, controls)	Exposure measurement	Results[a]		
USA, several states (Wynder et al., 1983)	Men (153, 5469) Women (122, 2525)	Daily alcohol intake	RR for drinkers of >5 oz daily versus nondrinkers men, 1.6 (0.9–2.6) women, 0.9 (0.3–2.1)		
France, Marseilles (Durbec et al., 1983)	Men (37, 100) Women (32, 99)	Daily ethanol intake in grams	RR for median drinkers (~40 g/day) versus nondrinkers, [2.4 (1.2–4.3)]		
Japan, Tokyo (Kodama & Mori, 1983a,b)	Men (59, 72) Women (25, 29)	Habitual daily consumption	RR for habitual drinkers versus others, [0.6 (0.3–1.2)]		
USA, Baltimore (Gold et al., 1985)	Men (94, 188) Women (103, 206)	Categorization into nondrinkers, drinkers (any amount or frequency)	No or inverse association		
USA, Los Angeles County (Mack et al., 1986)	Men (282, 282) Women (208, 208)	Daily ethanol intake in grams; total and from various sources	Alcohol (g/day) <40 40–79 >79	 0.7 (0.5–1.1) 0.8 (0.5–1.3) 1.2 (0.7–2.2)	
Sweden, Stockholm and Uppsala (Norell et al., 1986)	Men (55, 110) Women (44, 88)	Daily ethanol consumption in grams	Alcohol (g/day) 0–1 2–9 ≥10	vs hospital controls 1.0 0.5 (0.3–0.9) 0.5 (0.3–1.0) (90% CI)	vs population controls 1.0 0.7 (0.5–1.2) 0.6 (0.3–1.1)

[a]Relative risk (RR) with 95% confidence intervals, except where noted; [ ] when calculated by the Working Group

On the basis of a clinical series of 83 patients with cancer of the pancreas in New Orleans, USA, and a comparison series of 100 patients assembled independently and subsequently, Burch and Ansari (1968) speculated that chronic alcoholism may substantially increase the risk for pancreatic cancer. [The Working Group noted that this clinical study was not conducted as, and does not have the methodological characteristics of, a case-control investigation.]

In a large case-control study of all cancers in Paris, Schwartz *et al.* (1957, 1962; see description, p. 167) grouped 61 male cases of pancreatic cancer, primary liver cancer and cancers of the peritoneum and compared them with matched hospital controls. The proportion of alcoholics and the mean alcohol intake were almost identical in the two groups.

Using as background data the results from a large population survey of 122 261 adults in 29 health districts in Japan, Ishii *et al.* (1968) analysed information gathered by questionnaire from 475 patients with pancreatic cancer, hospitalized in 100 collaborating institutions. They reported an increased RR (~ 1.5) for drinkers of alcoholic beverages. [The Working Group noted that the statistical significance of the finding was not given and that differences in tobacco smoking between cases and controls were not accounted for in the analysis.]

In a case-control study in three US cities, Wynder *et al.* (1973a,b) compared 100 men and 42 women with adenocarcinoma of the pancreas with 200 men and 107 women with diseases not related to tobacco use. They found a slight, nonsignificant, dose-unrelated association between alcohol consumption and risk for pancreatic cancer [RR, 1.3].

There were 224 cases of pancreatic cancer in the study of Williams and Horm (1977; for description, see pp. 170-171), but total ethanol consumption could be assessed for only 91 male and 85 female cases. Among men, the data indicate an overall slight, nonsignificant positive association between ethanol consumption and pancreatic cancer risk after adjustment for age, sex, race, education and smoking (RR, 1.3). Among women there was no association with ethanol consumption (RR, 0.6).

In a study in Geneva, Switzerland, the age-standardized mean daily ethanol consumption of histologically confirmed cases of pancreatic cancer from Geneva University Hospital was 46 g for men and 13 g for women; the corresponding consumption figures among population controls (among whom participation was 70%) were 47 g for men and 12 g for women; the differences are nonsignificant [RR for drinkers *versus* nondrinkers, ~ 1] (Voirol *et al.*, 1980). In a later analysis of the same data and a few additional cases, Raymond *et al.* (1987) observed, however, a significantly increased risk among beer drinkers (RR, 2.9). [The Working Group noted that there was no *a priori* hypothesis with regard to beer and that several comparisons, including one of individual beverages, had been undertaken.]

Lin and Kessler (1981) carried out a case-control study on 109 patients with histologically confirmed pancreatic cancer from collaborating hospitals in five metropolitan areas of the USA; 15 of the cases were islet-cell tumours. Controls were patients without cancer matched 1:1 with the patients for sex, age, race and marital status. The patients tended to drink more wine (16.5% *versus* 8.3%; $p < 0.05$ for two or more glasses/day) than the controls. [The Working Group noted that patients with tobacco- and alcohol-related diseases were not excluded from the controls and that no information was given on how alcohol consumption was analysed.]

In a study on 367 patients (218 men, 149 women) with histologically verified cancer of the pancreas from 11 hospitals in Massachusetts and Rhode Island, USA, and 644 controls with diseases unrelated to use of tobacco or alcohol, MacMahon *et al.* (1981) found no evidence of an association between alcohol intake and pancreatic cancer risk; the overall age- and sex-adjusted RR for regular drinkers was calculated by the Working Group to be 0.9 when adjusted for tobacco (95% CI, 0.6-1.3), with no evidence of increased risk at any level of consumption or with any type of alcoholic beverage.

In a study on 50 patients (32 men, 18 women) with histologically verified cancer of the pancreas from five hospitals in Athens, Greece, and 206 hospital controls (172 men, 34 women) with diagnoses other than cancer or disease of the liver or pancreas, Manousos *et al.* (1981) found a statistically significant association between pancreatic cancer and cigarette smoking but no association with regular drinking of alcoholic beverages (>10 g ethanol daily). The RR, adjusted for age, sex and tobacco use, was 0.7 for regular drinkers in comparison with nondrinkers.

In a study in California, USA, based on review of the medical records of 116 histologically confirmed cases of pancreatic cancer (56 male, 60 female) from two medical centres, two controls, matched for sex, age, race, hospital and year of admission, were matched for every cancer case: one control with malignant disease, the other with nonmalignant disease (Haines *et al.*, 1982). No association was found between alcohol intake and risk for pancreatic cancer.

In a US study on 275 histologically confirmed incident cases of primary pancreatic cancer (153 male, 122 female) from 17 hospitals and 7994 hospital controls (5469 male, 2525 female) with diseases unrelated to tobacco and stratified for age and smoking, Wynder *et al.* (1983) found slight, dose-unrelated, nonsignificant associations between alcohol intake and pancreatic cancer. Heavy drinkers (≥15 oz [~120 g] ethanol/day) had tobacco-adjusted RRs of 1.6 among men and 0.9 among women, when compared to nondrinkers.

In a study of 69 histologically verified cases of adenocarcinoma of the pancreas (37 male, 32 female) from three gastroenterology departments in Marseilles, France, and 199 controls (100 male, 99 female) matched for sex, age and neighbourhood, without gastrointestinal diseases, Durbec *et al.* (1983) found, in a logistic conditional regression model, a positive association between total alcohol intake (particularly wine of high alcohol content) and pancreatic cancer risk [RR for drinkers *versus* nondrinkers, 2.4]. The RR was reduced after controlling for fat and carbohydrate intake, and there were unexpected negative associations with duration of alcohol consumption; there was no increased risk with regular drinking of aperitives and spirits. [The Working Group noted that these findings, the lack of association with tobacco smoking, and the unspecified participation rate among the potential controls make interpretation of the results difficult.]

In a study on 84 primary pancreatic carcinoma cases (59 male, 25 female) confirmed at autopsy and 113 randomly selected autopsy controls (72 male, 29 female) in Tokyo, Japan, Kodama and Mori (1983a,b) found no evidence for an increase in pancreatic cancer risk among regular drinkers of saké or other alcoholic beverages, on the basis of information derived from clinical records. The Working Group calculated a RR of 0.6 among habitual drinkers, not adjusted for smoking.

Gold *et al.* (1985) matched 94 male and 103 female cases of histologically confirmed pancreatic cancer from 16 hospitals in Baltimore, MD, USA, using an age-, race- and sex-matched case-control design, with both a hospital control series and a random-digit-dialling population control series. Proxy interviews were undertaken for 75% of the cases; controls were interviewed directly. No association was found between alcohol intake and cancer of the pancreas. The RR in comparison with the hospital controls was calculated by the Working Group to be 1.1 (0.7-1.7) and that in comparison with population controls to be 0.6. The inverse association was more evident among wine drinkers: the RR was calculated by the Working Group to be 0.9 (0.5-1.4) in comparison with hospital controls and 0.5 (0.3-0.8) with population controls.

In a population-based case-control study in Los Angeles, USA (Mack *et al.*, 1986), 282 male and 208 female cases of histologically confirmed pancreatic cancer in persons less than 65 years of age were identified from a cancer registry and compared with 282 male and 208 female matched neighbourhood controls. Information about alcohol intake was obtained by proxy interview for most cases and by personal interview for most controls. A nonsignificant inverse association was found between cancer of the pancreas and alcohol intake from any source; the inverse association was more pronounced for table wine consumption. The estimated RRs (*versus* nondrinkers) were 0.7 (0.5-1.1) for consumers of less than 40 g ethanol daily, 0.8 (0.5-1.3) for consumers of 40-79 g ethanol daily and 1.2 (0.7-2.2) for consumers of more than 79 g ethanol daily (not controlled for tobacco). No interaction between alcohol intake and smoking was evident.

A population-based case-control study in Sweden involved 55 male and 44 female cases of histologically confirmed cancer of the pancreas compared with an age- and sex-matched control series of hospital patients with inguinal hernia and another from the general population (Norell *et al.*, 1986). Inverse associations were noted in both comparisons, with RRs for frequent *versus* infrequent alcohol use of 0.5 (*versus* hospital controls) and 0.7 (*versus* population controls). The latter RR was calculated by the Working Group.

(*h*) *Cancer of the breast*

(i) *Cohort studies*

Four cohort studies in general populations have been published in which the association between alcohol intake and breast cancer has been examined (see Table 66).

Hiatt and Bawol (1984) followed 88 477 female members of the Kaiser Foundation health care plan in California (USA) who were more than 15 years of age at enrolment and had completed a questionnaire on the use of alcoholic beverages. Between 1960 and 1972, 1169 incident cases of breast cancer occurred; multivariate analysis was done on 694 cases over 30 years of age. After controlling for age, race, education, smoking, body mass index, cholesterol level and reproductive factors (all of which made only small differences), the

Table 66. Relative risks for breast cancer in cohort studies

Reference	Population	No. of cases	Alcohol consumption	Relative risk	95% confidence interval	Comment
Hiatt & Bawol (1984)	88 477 US health-plan members (1960-72); follow-up until 1977, aged >15 years	694	0 drinks/day	1.0		Controlled for race, education, smoking, body mass index, cholesterol, reproductive factors; no data on specific beverages
			<3 drinks/day	1.0		
			≥3 drinks/day	1.4	[1.0-1.7][a]	
Hiatt et al. (1987)	69 000 US health-plan members; five years of follow-up (1979-84)	303	Nondrinkers	1.0		Controlled for age, race, body mass index, smoking; effect not limited to any specific bevereage. RR highest among white and Hispanic and postmenopausal women
			Past drinkers	2.2	1.2-3.9	
			1-2 drinks/day	1.5	1.0-2.3	
			3-5 drinks/day	1.5	0.8-2.8	
			≥6 drinks/day	3.3	1.2-9.3	
Schatzkin et al. (1987)	USA, First National Health and Nutrition Examination Survey (1971-75); 7188 women 25-74 years of age; median follow-up, 10 years	121	No drinks in last year	1.0		Controlled for education, body mass index, dietary fat, reproductive factors; no data on specific beverage use; highest RR among youngest and thinnest women
			>0.1-1.2 g/day	1.4	0.8-2.5	
			1.3-4.9 g/day	1.6	0.9-3.1	
			≥5 g/day	2.0	1.1-3.7	
Willett et al. (1987)	USA, 89 538 registered nurses aged 34-59 years followed up for 4 years	601	0 g/day	1.0		Significantly increased RR independently for 5+ g/day of beer, 1.4 (1.1-1.8), liquor, 1.4 (1.1-1.7), but not wine, 1.1 (0.9-1.4). RR highest among thinner women and those without other risk factors for breast cancer (2.5; 1.5-4.2)
			<1.5 g/day	1.0	0.8-1.3	
			1.5-4.9 g/day	0.9	0.7-1.2	
			5.0-14.9 g/day	1.3	1.0-1.6	
			≥15 g/day	1.6	1.3-2.0	

[a] Calculated by the Working Group

SIRs were 1.0 for fewer than three drinks [not further specified] per day and 1.4 for three or more drinks per day. [The Working Group noted that, because of the way in which the question on alcohol use was asked, the authors were not able to divide the group consuming fewer than three drinks per day more finely, or to examine the effects of specific beverages.]

Hiatt *et al.* (1987) presented preliminary data in an abstract[1] on a separate cohort of 69 000 US women belonging to the same health care plan. During five years of follow-up (1979-84), 303 incident cases of breast cancer occurred. After controlling for age, race, body mass index and cigarette smoking, the SIRs were 1.5 for those consuming one to two drinks of any alcoholic beverage per day, 1.5 for those consuming three to five drinks per day, and 3.3 for those consuming six or more drinks per day. RRs were strongest among white and Hispanic and among postmenopausal women.

Schatzkin *et al.* (1987) analysed data from the first US National Health and Nutrition Examination Survey. At enrolment, 7188 women 25-74 years of age examined during 1971-75 were available for analysis. During a median of ten years of follow-up, 121 incident cases of breast cancer were diagnosed. After controlling for the effects of education, body mass index, dietary fat (based on a single 24-h recall) and reproductive factors, the adjusted RRs were similar or slightly higher than the crude relationships. When compared with women reporting no alcohol use during the previous year, the SIRs were 1.4 for women reporting an intake of <0.1-1.2 g ethanol per day, 1.6 for 1.3-4.9 g per day and 2.0 for ≥5 g per day. No data were available on the use of specific beverages. The highest SIRs were seen among the youngest and thinnest women.

Willett *et al.* (1987) examined the risk for breast cancer in relation to alcohol intake among members of the US Nurses' Health Study cohort. The alcohol intake of 89 538 registered nurses aged 34-59 years was assessed by questionnaire in 1980. The evaluation was validated by comparison with intake measured by a detailed day-by-day recording of all foods and beverages taken by a subgroup of 173 participants (see p. 154). In this study, comprehensive data on other dietary factors, including dietary fat, protein, fibre and vitamin A were also collected. During a follow-up of four years, 601 incident cases of breast cancer were ascertained. In comparison with women reporting no alcohol intake during the year prior to the baseline questionnaire, the RRs controlled for reproductive factors were 1.0 for <1.5 g ethanol per day, 0.9 for 1.5-4.9 g/day, 1.3 for 5.0-14.9 g/day and 1.6 for ≥15 g/day (Mantel extension χ for linear trend, 4.2; $p < 0.0001$). Controlling for nutritional factors as well as for family history of breast cancer and reproductive variables had no influence on the association of alcohol with risk for breast cancer. When the use of ≥5 g ethanol per day from specific alcoholic beverages was examined, controlling for the use of other alcoholic beverages simultaneously in a multivariate model, significant associations were found for beer (RR, 1.4) and spirits (1.4), but not for wine (1.1). For the latter, the CI includes the estimates for the other beverages, indicating that an association with wine is still quite plausible. The association with breast cancer risk was strongest among the women who were 45-54 years old and thinner. The relationship between alcohol intake and breast

[1]Subsequent to the meeting, this study was published in full (Hiatt *et al.*, 1988).

cancer tended to be somewhat stronger among current and past smokers than among those who had never smoked; however, this difference in RR was not significant. A particularly strong association was observed among those consuming 15 g or more ethanol per day and who had no other risk factor for breast cancer (RR, 2.5). Information on earlier alcohol intake was not collected; however, no elevation in risk for breast cancer was seen among women who were currently nondrinkers and reported that their alcohol intake had greatly decreased during the previous ten years. The authors noted that differential detection of breast cancer among alcohol users was unlikely to explain the positive associations because the percentage of cases with metastases in one or more lymph nodes was similar among the users and nonusers of alcohol.

(Descriptions of studies of cancers at many sites are given on pp. 158-164).

In the Framingham Heart Study (Gordon & Kannel, 1984), 28 deaths from breast cancer were ascertained. A small, nonsignificant, negative logistic regression coefficient was noted for alcohol intake. [The Working Group noted the small number of cases and the limited analysis.]

In the Kaiser-Permanente Study (Klatsky *et al.*, 1981), a total of 11 deaths from breast cancer was found; no relationship with alcohol consumption was detected. [The Working Group noted that the number of cases was too small to examine the relationship with alcohol intake.]

Adelstein and White (1976) identified 475 women in the UK Alcoholics Study and ascertained deaths for a period of up to 21 years. Ten deaths due to breast cancer occurred compared with an expected number of 4.9, yielding a SMR of 2.0. No control for confounding effects was possible.

A few breast cancer deaths were reported in the other cohort studies on alcoholics: Schmidt and deLint (1972), two cases; Monson and Lyon (1975), three cases (4.1 expected).

(ii) *Case-control studies*

Case-control studies of alcohol and breast cancer are summarized in Table 67.

In the study by Williams and Horm (1977; see description, pp. 170-171), 1167 breast cancer cases were reported, 1118 with known smoking and drinking habits. Data on other risk factors for breast cancer were not available. Overall, for women consuming less than 51 oz [<1200 g ethanol]-years, the RR was 1.3 ($p < 0.05$), and that for women consuming 51 or more oz-years was 1.6 ($p < 0.01$). For women consuming less than 51 and 51 or more oz-years of specific beverages, the RRs were 1.7 ($p < 0.01$) and 1.1 for wine, 1.2 and 1.4 for beer, and 1.4 ($p < 0.01$) and 1.4 ($p < 0.05$) for spirits. [The Working Group noted that the relationships with specific beverages were not controlled for the use of other alcoholic beverages, with which they tend to be highly correlated.]

Rosenberg *et al.* (1982) utilized data from a large drug-surveillance programme conducted in Canada, Israel and the USA to examine the relationship between alcohol intake and breast cancer risk. They identified 1152 incident cases (30-69 years old) and compared their alcohol use with that of two control series: 519 women with endometrial or ovarian cancer and 2702 women hospitalized for nonmalignant diseases. Drinkers of each

Table 67. Summary of results of case-control studies of breast cancer and alcohol intake

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)[b] (95% confidence interval)					Comments
USA, Multicenter (Williams & Horm, 1977)	1118, 3178		None	Total	Wine	Beer	Spirits	Controlled for smoking, age, race
		<50 oz [1200 g]-year	1.0	1.3*	1.7*	1.2	1.4*	
		≥51 oz [1200 g]-year	1.0	1.6*	1.1	1.4	1.4*	
			None	Total	Wine	Beer	Spirits	
Canada, Israel, USA (Rosenberg et al., 1982)	1152, 519 endometrial or ovarian cancer	<4 days/week	1.0	1.5 (1.1-2.1)	1.8*	2.0*	1.2	Control for educational level and reproductive factors had minimal effect on RR
		≥4 days/week		2.0 (1.3-2.0)	2.3	2.2	2.1*	
		Ex-drinker		1.3 (0.7-2.3)				
	1152, 2702 nonmalignant disorders	<4 days/week	1.0	1.9 (1.5-2.4)	2.2*	1.2	1.1	
		≥4 days/week		2.5 (1.9-3.4)	1.9*	2.1*	2.5*	
		Ex-drinker		1.6 (1.1-2.4)				
USA, Roswell Park, NY (Byers & Funch, 1982)	1314, 770	0 drinks/months (never)	1.0					No relation with beer, wine, spirits
		0 drinks/month (ex)	0.6					
		<3 drinks/month	1.1					
		3-8 drinks/month	1.0					
		9-25 drinks/month	1.1					
		≥26 drinks/month	1.1					
USA (Paganini-Hill & Ross 1983)	239, 239	Never drink	1.0					No relation with beer, wine, spirits
		≤1 drink/day	1.0					
		≥2 drinks/day	1.0					
USA (Begg et al., 1983)	997, 730	0 drinks/week	1.0					Adjusted for age and smoking
		1-7 drinks/week	0.9 (0.8-1.1)					
		>7 drinks/week	1.4 (0.9-2.0)					

Table 67 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)[b] (95% confidence interval)	Comments
USA (Webster, L.A. et al., 1983)	1226, 1279	0 g/week	1.0	Alcohol questions not clearly directed to period before diagnosis; no effect of beer, wine, spirits
		<50 g/week	0.9 (0.7–1.2)	
		50–149 g/week	0.9 (0.7–1.2)	
		150–199 g/week	1.1 (0.7–1.7)	
		200–249 g/week	1.1 (0.7–1.9)	
		250–299 g/week	1.0 (0.5–1.7)	
		≥300 g/week	1.1 (0.6–1.8)	
France (Lê et al., 1984)	1010, 1950	Alcohol with meals	None 1.0; Total 1.5*; Cider 1.5; Beer 2.4*; Wine 1.4*	Matched for all characteristics; unknown participation rates; control for reproductive factors and dairy products did not affect risk
	500, 945		Total alcohol	
		0 g/week	1.0	
		1–79 g/week	1.0 (0.7–1.4)	
		80–159 g/week	1.4 (1.0–2.0)	
		160–239 g/week	1.5 (1.0–2.1)	
		≥240 g/week	1.2 (0.7–2.0)	
Northern Italy (Talamini et al., 1984)	368, 373	Ever versus never	2.5 (1.7–3.7)	High participation rates, controlled for education, occupation and reproductive factors
		Wine: no use	1.0	
		<0.5 l [~50 g 100% ethanol]/day	2.4 (1.6–3.5)	
		≥0.5 l/day	16.7 (3.1–89.7)	
Milan, Italy (La Vecchia et al., 1985)	437, 437	0 drinks/day	1.0	High participation rates, adjusted for reproductive factors, social class and years of education and limited dietary variables. Effect strongest among 40–49-years old
		≤3 drinks/day	1.3 (0.9–1.8)	
		>3 drinks/day	2.1 (1.1–4.0)	
		wine:		
		0 drink/day	1.0	
		≤3 drinks/day	1.2 (0.9–1.6)	
		>3 drinks/day	2.2 (1.1–4.7)	
		beer: any use	1.3 (0.8–2.1)	
		spirits: any use	1.4 (0.9–2.2)	

Table 67 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption[a]	Relative risk (RR)[b] (95% confidence interval)	Comments
USA, North Carolina (O'Connell et al., 1987)	276, 1519	<1 drink/week ≥1 drink/wee	1.0 1.5 (1.0-2.1) premonopausal women, 1.9 (1.1-3.3) postmenopausal women, 1.2 (0.7-2.0)	Adjusted for race, oestrogen use, oral contraceptive use, cigarette smoking; no specific data on beverages
USA (Harvey et al., 1987)	1524, 1896	Never 0.1-13 g/week 14-91 g/week 92-182 g/wee >183 g/week	1.0 1.1 (0.9-1.3) 1.1 (0.9-1.3) 1.3 (1.0-1.7) 1.7 (1.2-2.4)	Controlled for income, education and reproductive factors; effect almost entirely attributable to alcohol before age 30; independent effects of beer and spirits
Greece (Katsouyanni et al. 1986)	120, 120	Alcohol intake	Nonsignificant inverse trend	Low power; alcohol consumption levels not provided
Chile (Medina et al., 1983)	76, 76	None Occasional Moderate Not specified	1.0 0.8 (0.4-1.8) 2.8 (0.7-10.9) 1.9 (0.5-6.7)	No adjustment for potential confounders

[a] g = 100% ethanol
[b] *, significant

specific beverage were asked whether they consumed that beverage on fewer than four or on more than four days per week. Using the cancer series as a control group, women drinking on fewer than four days per week experienced a RR of 1.5 compared with nondrinkers; the corresponding RR for those drinking four or more drinks per day was 2.0. With the nonmalignant series as the control group, the RR was 1.9 for fewer than four days per week and 2.5 for four or more days per week. Control for years of education and reproductive variables in multiple logistic regression analysis did not alter the relationship of alcohol use with breast cancer appreciably. When examined by specific beverage type, similar RRs were observed for beer, wine and spirits. [The Working Group noted that these were not controlled for correlated use.]

Byers and Funch (1982), responding in a letter to the report of Rosenberg *et al.*, provided data from a large case-control study conducted in Roswell Park Memorial Hospital in the USA during 1957-65. The drinking habits of 1314 incident cases of breast cancer (30-69 years old) were compared with those of 770 patients with nonneoplastic conditions who attended the same institution. These investigators found no relationship between breast cancer risk and alcohol use at any level, nor with consumption of beer, wine or spirits. The authors noted that their subjects had been raised in a rural area during the Prohibition era, which may have resulted in the observed low level of alcohol consumption.

Paganini-Hill and Ross (1983), also in a letter responding to the report of Rosenberg *et al.*, described the relationship between alcohol intake and breast cancer in a US retirement community in California. These authors identified 239 prevalent cases and compared their current alcohol intake with that of 239 matched community controls of similar social class. No elevation in risk was found for those consuming one or more drinks per day, and no association was found with either wine, beer or spirits. A subsample of 25 cases reported that they had not reduced their alcohol intake after the diagnosis of cancer.

In another letter following the report of Rosenberg *et al.*, Begg *et al.* (1983) compared the alcohol use among 997 breast cancer cases ascertained as part of the US Eastern Cooperative Oncology Group with that among 730 patients with other malignancies not thought to be related to alcohol use. After adjustment for age and smoking, the RRs were 0.9 for one to seven drinks per week and 1.4 for seven or more drinks per week (not significant).

Webster, L.A. *et al.* (1983) examined the relation between alcohol use and breast cancer in a large, multicentred US case-control study based on tumour registries that was primarily designed to address the effect of steroid hormone use on risk for this disease. Cases consisted of 1226 women, 20-54 years old, who were compared with 1279 controls identified by random digit telephone dialling. The response rates for interview were 82% for cases and 85% for those identified as potential controls. [The Working Group noted that the number of controls who were not contacted at all is never known when using the random-digit dialling procedure.] Women were first asked whether they had consumed any alcoholic beverage during the preceding five years. Those responding positively were then asked about their usual consumption of beer, wine and spirits. The authors noted that both the cases and controls reported intakes that were higher than those noted in national surveys. No relationship between alcohol use and breast cancer risk was observed; even for use of more than 300 g ethanol per week, the RR was only 1.1. No association with beer, wine or spirits was seen. [The Working Group noted that, since the cases were identified through tumour registries and were thus interviewed several months after diagnosis, it is possible that they had reduced their intake due to their disease and that this was reflected in their responses to questions about current intake; the questions on the amount of alcohol consumed were not specifically directed to the period before the diagnosis of breast cancer.]

In a study in France, Lê *et al.* (1984, 1986) reported on the association of alcohol use with breast cancer risk among patients attending 66 private surgical clinics. A simple measure of alcohol intake (whether or not it was usually consumed with meals) was available for the entire group of 1010 incident cases and 1950 clinical controls. A positive relationship with breast cancer risk was observed (RR, 1.5; $p = 0.0001$); controlling for the effects of reproductive factors and a limited set of dietary questions (mainly on consumption of dairy products) did not appreciably alter this finding (RR, 1.9; 1.4-2.6). Additional detailed questions on alcohol use were subsequently posed to the remaining 500 cases and 945 control women.The RRs were 1.0 for 1-79 g ethanol/week, 1.4 for 80-159 g/week, 1.5 for 160-239 g/week and 1.2 for 240 or more g/week. In this population, most alcohol was taken in the form of wine. A significant elevation in risk was also associated with beer consumption; no significant association was found for alcohol in the form of cider, but the use of this beverage was relatively low.

Talamini *et al.* (1984) conducted a case-control study in a northern Italian population that included information on the use of wine, the primary form of alcohol consumed in that area. They identified 368 cases (27-79 years old); controls consisted of 373 women hospitalized with acute conditions. Participation rates were 98% for both cases and controls. Multivariate analyses were used to control for the effects of education, occupation and reproductive variables; these analyses did not appreciably alter the crude relationships. In comparison with nondrinkers, the RR for use of <0.5 l of wine per day [~ 50 g ethanol] was 2.4, and for use of ≥0.5 l of wine per day, the RR was 16.7.

In another study from northern Italy, La Vecchia *et al.* (1985) obtained information on the number of drinks of specific alcoholic beverages per day from 437 incident cases of breast cancer (26-74 years old) and 437 patients hospitalized with acute conditions. Analyses were conducted adjusting for social class, years of education and reproductive variables. For women consuming three or fewer drinks per day, the RR was 1.3, and for those drinking more than three drinks per day it was 2.1. For consumption of more than three drinks of wine per day, the RR was 2.2. The effect was strongest for women 40-49 years old: RR of 3.5 for more than three drinks/day.

In a study from North Carolina, USA, O'Connell *et al.* (1987) studied alcohol intake among 276 incident cases and 1519 community controls. Analyses were adjusted for race, oestrogen use, oral contraceptive use and cigarette smoking. For women consuming one or more drinks of any alcoholic beverage per week compared with those consuming none or less than one drink per week, the RR was 1.5. No data on specific beverages were available. In this study, the effect of alcohol was limited to premenopausal women, among whom the RR was 1.9, as compared with 1.2 among postmenopausal women.

Harvey *et al.* (1987) conducted a nested case-control study within a population of participants in a national US cancer screening programme. A total of 1524 incident cases of breast cancer were identified in white women that had been diagnosed at least three years after entry into the screening programme. A total of 1896 control subjects were identified from among participants who did not develop cancer. In comparison with women who had never drunk alcohol, the RR was 1.1 for drinking 0.1-13 g ethanol per week, 1.1 for 14-91 g/week, 1.3 for 92-182 g/week and 1.7 for ≥183 g/week. Controlling for education, income and reproductive factors did not appreciably affect the RRs. Independent associations were observed for consumption of ≥92 g/week beer (RR, 1.7) and spirits (2.1) but not for wine (0.8). The authors noted that the lack of effect of wine may have been due to the small number of wine drinkers. The influence of alcohol use at different ages was examined in this study; the positive association with breast cancer was entirely attributable to alcohol use before the age of 30. For women who consumed >92 g ethanol per week before age 30, the risk for breast cancer was elevated whether or not they drank at later ages. However, the number of women who drank before age 30 and later stopped was small (15 cases), so that the distinction between those who continued and those who stopped is unstable. For alcohol consumption at less than 30 years of age, the association with risk for breast cancer did not vary by age at diagnosis, suggesting that a latent period effect was not present.

[The Working Group noted that in the studies of O'Connell *et al.* (1987) and Harvey *et al.* (1987) hospital or clinic controls were not used. Thus, the possibly lower alcohol consumption of hospital controls relative to members of the community at large (Anon., 1985b) is an unlikely explanation for the positive associations found between breast cancer and alcohol use.]

In a small case-control study in Greece of 120 cases and 120 orthopaedic patients as controls, Katsouyanni *et al.* (1986) observed a nonsignificant inverse relationship between alcohol intake and risk for breast cancer. [The Working Group noted that alcohol intake was not a focus of this study and few details are provided; levels of alcohol intake were not described.]

Medina *et al.* (1983) reported a small, hospital-based case-control study of breast cancer in Chile. Controls were patients hospitalized for cholecystectomy and matched by age with cases; 76 pairs were interviewed. In comparison with nondrinkers, moderate alcohol users (not defined) experienced a nonsignificant elevation in risk for breast cancer (RR, 2.8).

(iii) *Risk associated with type of alcoholic beverage*

In ten of the studies, data were collected on intake of specific alcoholic beverages. Wine intake was significantly associated with breast cancer in five studies (Williams & Horm, 1977; Rosenberg *et al.*, 1982; Lê *et al.*, 1984; Talamini *et al.*, 1984; La Vecchia *et al.*, 1985); beer intake was significantly associated with increased risk in four (Rosenberg *et al.*, 1982; Lê *et al.*, 1984; Harvey *et al.*, 1987; Willett *et al.*, 1987); and intake of spirits was significantly associated with increased risk in four (Williams & Horm, 1977; Rosenberg *et al.*, 1982; Harvey *et al.*, 1987; Willett *et al.*, 1987). Byers and Funch (1982), Paganini-Hill and Ross (1983) and Webster, L.A. *et al.* (1983) found no association with consumption of beer, wine or spirits.

The examination of the effects of specific beverages is complicated by the tendency among women, at least in some populations, to drink more than one type of alcoholic beverage. The effects of specific beverages are thus best studied using multivariate analyses in which the use of each beverage is controlled for use of the others. Only in the studies of Harvey *et al.* (1987) and Willett *et al.* (1987) was this form of analysis used; both showed significant independent effects of beer and spirits but not of wine. Although the effect of wine appears to be less than that of beer or spirits, the CI for wine drinking included the estimate for the other two beverages, precluding a firm conclusion about the effect of wine.

(iv) *Studies of joint exposure*

In most reports, data have not been included on the effects of joint exposures, and in those in which they were, the subgroups analysed differed. Age and menopausal status have been examined most commonly in connection with alcohol use, and, because of their high correlation, these variables are not distinguished for this purpose. Of the six studies that examined this association (La Vecchia *et al.*, 1985; Harvey *et al.*, 1987; Hiatt *et al.*, 1987; O'Connell *et al.*, 1987; Schatzkin *et al.*, 1987; Willett *et al.*, 1987), four found a higher RR among younger or premenopausal women, one showed no evidence for an interaction (Harvey *et al.*, 1987), and one found a higher RR among postmenopausal women (Hiatt *et al.*, 1987). The only other suggestion of an interaction, which has been observed in more than one study, is the observation of a higher RR among thin women (Schatzkin *et al.*, 1987; Willett *et al.*, 1987). Expressing alcohol intake in dose per kilogram of body mass did not appreciably alter the relation of alcohol intake with risk for breast cancer in the latter study. The RRs tend to be somewhat higher among women with no other risk factor for breast cancer; as noted previously, the RR was 2.5 for ≥15 g ethanol per day among women with no other risk factor compared with the RR of 1.5 among other women (Willett *et al.*, 1987).

(*i*) *Cancer of the lung*

(i) *Cohort studies* (descriptions of studies of cancers at many sites are given on pp. 158-164)

Data from cohort studies on alcohol consumption and lung cancer are summarized in Tables 68 and 69.

In the study of Norwegian alcoholics (Sundby, 1967), 19 lung cancer deaths were observed with 13.2 expected on the basis of mortality figres for Oslo. No information on tobacco use was available, but the SMR for bronchitis was 2.3 when compared with Norwegian rates. In the study of Pell and D'Alonzo (1973), described on p. 210, five cases of lung cancer were observed in alcoholics and two in controls.

In the study of US veterans (Robinette *et al.*, 1979), mortality from lung cancer in alcoholics was no different from that in nasopharyngitis controls (64 and 66 deaths, respectively). Mortality from respiratory diseases as a whole, however, was significantly higher than in white US men (SMR, 1.36; $p < 0.01$). [The Working Group noted that smoking was not controlled for.]

Table 68. Relative risks (RR) for lung cancer in cohort studies without individual control of tobacco use

Study and reference	No. of subjects	RR[a]	Comments
Norwegian Alcoholics (Sundby, 1967)	19 deaths	3.5* 1.4	Compared with Norwegian population Compared with Öslo population
USA (Pell & D'Alonzo, 1973)	5 deaths	2.5	Two deaths among one-to-one matched controls
US Veterans Alcoholics (Robinette et al., 1979)	64 deaths	1.1 (90% confidence interval, 0.8-1.4)	
Finnish Alcohol Misusers (Hakulinen et al., 1974)	200 cases	2*	Expectancy (99.2) computed from whole population rates, but observed drawn from only the first third of the cohort in alphabetical order
Finnish Alcoholics (Hakulinen et al., 1974)	33 cases	1.6*	
Massachusetts Alcoholics (Monson & Lyon, 1975)	19 deaths	1.3	
UK Alcoholics (Adelstein & White, 1976)	44 deaths	Men: 1.0 Women: 3.2*	
Dublin Brewery Workers (Dean et al., 1979)	98 deaths	1.1 (0.9 if socio-economic status adjusted for)	Smoking was forbidden at the brewery for many years; according to relatives, 26 of 45 deceased smoked 23 cigarettes per day on average
Japanese Prospective Study (Hirayama, 1979)	611 deaths	Drinking / Smoking / RR Daily / Daily / 5.5 Occasionally / Daily / 4.7 No / Daily / 5.4 Not daily / No / 1.0	Actual numbers not stated

Table 68 (contd)

Study and reference	No. of subjects	RR[a]	Comments
Danish Brewery Workers (Jensen, 1980)	287 cases 280 deaths	1.2	Excess of the same order as for mineral-water bottlers (who did not have the right to free beer, data not shown) and as excess expected among persons of low socioeconomic class in Denmark
Canadian Alcoholics (Schmidt & Popham, 1981)	89 deaths	1.7, compared with Ontario population 1.0, compared with US veterans who smoked 21-29 cigarettes/day	Only 2% of cohort were lifetime nonsmokers, 94% were current smokers and 88% smoked >20 cigarettes/day

[a]*, significant

Table 69. Relative risks (RR) for lung cancer in cohort studies with quantitative information on consumption and individual control for tobacco use

Study and reference	Results			Comments
Kaiser Permanente (Klatsky *et al*., 1981)	Usual no. of drinks/day in the last year	No. of lung cancer deaths and % mortality	RR	Among nonsmokers, the proportion of ex-smokers increases significantly with alcohol consumption, as well as the proportion of heavy smokers in the category of presently smoking. Furthermore, heavy drinkers include a 'slightly larger fraction who had smoked for over 20 years and of persons who inhaled' [data not shown]. Residual confounding highly probable
	0 (and ex-drinkers)	15 0.75%	1.0	
	≤2	7 0.35%	0.5	
	3-5	16 0.79%	1.1	
	≥6	24 1.19%	1.6*	
Norway (Kvåle *et al*., 1983)	Vit. A index	No.	RR	RR for highest *versus* low current alcohol intake by vitamin A index, adjusted for age, smoking, geographical region, urban/rural residence and socio-economic status. Paper focuses on vitamin A and not on alcohol; a table refers to 65 histologically verified cases, but the overall incidence was 168
	Low	25	3.7	
	Medium	21	1.4	
	High	19	0.2	
	Total	65	1.3	
Framingham Study (Gordon & Kannel, 1984)	On the basis of 42 male and 9 female lung cancer deaths, a positive association (among males only) with level of alcohol consumption disappears after controlling for cigarettes/day, age, blood pressure, relative weight and lipoproteins			Ex-drinkers are grouped with nondrinkers; paper focuses on overall mortality and the categorization of alcohol consumption for studying cancer is not reported.

Table 69 (contd)

Study and reference	Results				Comments
Hawaiian-Japanese (Pollack *et al.*, 1984)	Usual monthly alcohol consumption (oz/month)	Age- and tobacco-adjusted incidence	RR		Alcohol used: 10% wine, 3.7% beer, 38% whisky. Crude data not shown, so importance of tobacco confounding and likelihood of residual confounding cannot be assessed. Incidence per 100 000 person-years, based on 89 incident cases confirmed by histological study
	None	70.1	1.00		
	<5	47.5	0.68		
	5–14	91.3	1.30		
	15–39	120.2	1.72		
	≥40	130.5	1.86		
Japanese Doctors (Kono *et al.*, 1986)	Drinking habit	No. of deaths	Age-adjusted death rate	Age- and tobacco-adjusted RR	Apparent dose-effect relationship among consumers cannot be explained by residual tobacco confounding since there is no tobacco confounding.
	Never	24	11.5	1	
	Ex-drinker	5	5.4	0.6 (0.2–1.5)	
	Occasional	12	4.9	0.4* (0.2–0.8)	
	<43 mg/day	17	9.2	0.8 (0.4–1.4)	
	≥43 mg/day	16	12.4	0.9 (0.5–1.7)	

In the Finnish study of alcoholics and alcohol misusers study (Hakulinen *et al.*, 1974), 200 cases of lung cancer were detected in alcohol misusers while 99 were expected (SIR, 2.0); 33 cases were observed among chronic alcoholics with 20.2 expected (SIR, 1.6). [The Working Group noted that, if the high RRs for alcohol misusers were due to confounding by tobacco, there would have been extreme differences in the smoking habits of the misusers and the control population; a lower SIR was seen for the alcoholics, who certainly drank more heavily than the misusers.]

In the study of Massachusetts alcoholics (Monson & Lyon, 1975), the proportionate cancer mortality ratio for lung cancer was 1.3, based on 19 lung cancer deaths. [The Working Group noted that there was no adjustment for smoking.]

In the UK follow-up study of alcoholics (Adelstein & White, 1976), a significant excess of lung cancer deaths was observed in women (8 *versus* 2.5 expected) but not in men (36 *versus* 35.3). [The Working Group noted that information on tobacco use was not available.]

In the study of Dublin brewery workers (Dean *et al.*, 1979), the SMR for lung cancer, adjusted for socioeconomic level, was 0.9.

In the Japanese prospective study (Hirayama, 1979), an analysis of the effect of drinking alcoholic beverages (none, occasionally, daily) in daily smokers was based on 611 deaths from lung cancer among men. The SMRs (compared with men who did not smoke or drink daily) were 5.4, 4.7 and 5.5, respectively, indicating no variation in relation to alcohol drinking. In a further analysis of 1324 lung cancer deaths observed in 16 years of follow-up of 122 261 males (Hirayama, 1985), the SMR associated with alcohol consumption [not otherwise defined], adjusted for tobacco, was 1.6. [The Working Group noted that the levels of exposure to alcohol and tobacco were not defined.]

In the study of Danish brewery workers (Jensen, 1980), both the SMR and SIR for lung cancer were 1.2 (95% CI, 1.0-1.3). The excess was of the same order among beer production workers (SIR, 1.1) and mineral-water bottlers (SIR, 1.3), was independent of duration of employment, and corresponded with expected social class differences. No data on smoking were provided, but the SMR for bronchitis was less than 1, indicating that smoking rates were not higher than in the general population.

In the study of Canadian alcoholics (Schmidt & Popham, 1981), the SMR for lung cancer was 1.7 ($p < 0.01$) in comparison with the population of Ontario; however, in comparison with the stratum of US veterans who most closely resembled the alcoholics in their smoking habits (21-39 cigarettes per day), the SMR for lung cancer was 1.0.

In the Kaiser-Permanente study (Klatsky *et al.*, 1981), cumulative mortality from lung cancer over ten years' follow-up was 0.7% (15 deaths) in persons consuming no drinks per day, 0.4% (7 deaths) in those consuming two or fewer, 0.8% (16 deaths) in those taking three to five, and 1.2% (24 deaths) in those taking six or more drinks per day. The authors noted that, although the groups were matched for smoking status, the group of heavy drinkers included more individuals who smoked heavily and the group of nondrinkers more individuals who had never smoked. [The Working Group noted that, although there was a significant difference between the two lowest consumption groups and the highest, the reported residual confounding by tobacco makes interpretation difficult.]

In a prospective cohort study on the effects of dietary vitamin A on lung cancer (Kvåle *et al.*, 1983) in Norway, in which 13 785 men and 2928 women were followed for 11.5 years, 168 incident cases of lung cancer were diagnosed. Alcohol use was analysed in a subset of the cohort in which the relevant information on consumption of alcohol, tobacco and vitamin A was available. The relative odds ratios estimated for the highest of three levels of alcohol consumption [groups not defined] *versus* the lowest were 3.7, 1.4, 0.2 and 1.3 for low, medium and high vitamin A index groups and for the whole group, respectively. The figures were based on 65 cases and were adjusted for age, cigarette smoking (never, ex-, current smokers of 1-19 and ≥20 cigarettes/day), region and urban/rural residence and socio-economic group.

In the Framingham study (Gordon & Kannel, 1984), 42 deaths from lung cancer deaths were observed in men. There was a nonsignificant association between lung cancer and alcohol consumption; but even this disappeared in logistic regression analysis, standardized for number of cigarettes per day, systolic blood pressure, age, relative weight and plasma lipoprotein levels. Only nine deaths from lung cancer were observed among women.

In the study of Hawaiian Japanese (Pollack *et al.*, 1984), with 89 incident cases of lung cancer, age- and smoking-adjusted incidence rates of lung cancer showed a significantly positive trend with total alcohol consumption. The SIRs compared with abstainers were 2.2 for those drinking at least 1.5 l of wine/month and 2.6 for those who drank at least 1.5 l of whisky/month; these were significantly elevated. Tobacco was controlled for by classifying smoking habits as never, former and current smokers; the results were the same when the subjects were classified into nonsmokers and current smokers, further subdivided according to the amount smoked (data not shown). The authors could not exclude the possibility that the apparent association between lung cancer and alcohol consumption was due to residual confounding by tobacco.

In the study of Japanese doctors (Kono *et al.*, 1986), there were 74 deaths from lung cancer. Nondrinkers had the highest SMR for lung cancer; among the drinkers, the SMRs rose with increasing alcohol consumption and were 0.6 for ex-drinkers, 0.4 for occasional drinkers, 0.8 for drinkers of <2 *go* [43 g ethanol] per day and 0.9 for drinkers of >2 *go* per day. Confounding by tobacco was controlled for by classifying smoking habits into five categories (non-, ex- and current smoker consuming 1-9, 10-19, 20+ cigarettes/day). [The Working Group considered that the observed dose-response effect among current drinkers is unlikely to reflect residual confounding by smoking, since adjustment for smoking had little effect on the estimates of alcohol-related RR.]

Three of the cohort studies described above (Klatsky *et al.*, 1981; Pollack *et al.*, 1984; Kono *et al.*, 1986) provide some information on the smoking-adjusted risk for lung cancer at various levels of alcohol consumption. There was a consistent pattern of decreased risk at low levels of alcohol consumption compared to non-/never drinkers and, among consumers, an increasing trend in risk with increasing level of consumption. In general, within each study, differences in risk associated with different levels of consumption are not statistically significant. Overall, the apparent increase in risk with increasing level of consumption is most likely to be attributable to residual confounding.

(ii) *Case-control studies*

Data from case-control studies on the association between alcohol consumption and lung cancer incidence are summarized in Table 70.

In a study on cancer incidence in North Wales and Liverpool, UK, in relation to habits and environment (Stocks, 1957; for description, see p. 206), the association of beer drinking with risk for lung cancer was studied by interviewing 485 male lung cancer patients aged 45-74 years, or their family members, and 4630 controls matched for age and area of residence. Of the cases, 328 were daily or weekly beer drinkers, while 273.0 would have been expected; the association was limited to those who smoked fewer than 100 cigarettes per week. [The Working Group noted that confounding could not be excluded.]

In a large case-control study in Paris, France (Schwartz *et al.*, 1962; for description, see p. 167), a significant difference was seen in the alcohol consumption of 1159 cases with bronchial cancer and that of 1196 controls with tobacco-unrelated cancers; this almost disappeared, however, after adjustment for smoking.

In a hospital-based case-control study in Durban, South Africa (Bradshaw & Schonland, 1969), 45 lung cancer patients and 341 controls without malignant disease were interviewed with regard to their alcohol consumption (use of Bantu beer, European spirits or local concoctions). A significantly greater number of cases than controls were consumers of local concoctions (53.3 *versus* 24.9%). [The Working Group noted that no adjustment was made for smoking habits or for age.]

Keller (1977) compared the relative frequency of lung cancer among patients discharged from the US complex of veterans' hospitals with cirrhosis and any cancer (286 men) with the relative frequency among patients without cirrhosis and any cancer (374 men). The frequency was not increased over that in patients without cirrhosis, even when cancers of the mouth, pharynx and digestive organs were excluded.

In the patient interview study of Williams and Horm (1977; for description, see pp. 170-171), an association was seen between the level of wine, beer, spirits or total ethanol consumption and lung cancer in both men and women. This association disappeared completely, however, when the analysis was performed on a subgroup for which the data allowed controlling for smoking (568 male and 155 female cases).

In a case-control study in Dublin, Ireland (Herity *et al.*, 1982), the alcohol consumption of 68 lung cancer patients was compared with that of a control group used in a previous study (Herity *et al.*, 1981) that examined the association between alcohol consumption and cancer of the larynx (see description, p. 184). The odds ratio of those with heavy alcohol consumption (in excess of 90 g ethanol per day for ten years) compared to non- and light drinkers was 2.1. The risk was greatly reduced, however, when alcohol intake was considered in the context of tobacco smoking (fewer than 20 cigarettes/day, 20 or more cigarettes/day). The authors concluded that the results were attributable almost entirely to confounding.

Table 70. Summary of results of case-control studies of lung cancer and alcohol intake

Place (reference)	Subjects (cases, controls)	Alcohol consumption	Results[a]					Comments
France, Paris (Schwartz et al., 1962)	Men (1159, 1196)	Mean alcohol consumption based on wine, cider, beer and spirits consumed over the last ten years	Highly significant difference (135 ml/day versus 113; X^2, 42.5) decreases dramatically when cigarettes/day controlled for (X^2, 5.8)					Authors considered that, with further adjustments, the significance of the association would disappear.
South Africa, Durban (Bradshaw & Schonland, 1969)	Men (45, 341)	User/nonuser of beer/European spirits or concoctions	More cases than controls were users of local concoctions					No individual control for tobacco use
USA, Multicenter (Williams & Horm, 1977)	Men (737, 2102)			Men Age-adj.	Men Age- & tobacco-adj.	Women Age-adj.	Women Age- & tobacco-adj.	RR for drinkers versus nondrinkers
	Men, adjusted for smoking (568, 2102)		Wine <50 oz-yr	0.9	0.6	0.9	0.7	
	Women (194, 3464)		≥51 oz-yr	1.4	1.1	1.8	1.1	
	Women, adjusted for smoking (155, 3464)		Beer <50 oz-yr	1.3	1.2	1.6	0.8	
			≥51 oz-yr	1.7*	1.1	2.3*	1.1	
			Spirits <50 oz-yr	1.2	0.9	1.7*	1.2	
			≥51 oz-yr	1.6*	1.1	1.3	0.6	
			Ethanol <50 oz-yr	1.2	0.9	1.5	1.1	
			≥51 oz-yr	1.6*	1.0	1.5	0.7	
Ireland, Dublin (Herity et al., 1981)	Men (59, 152)	Median lifetime exposure (90 g ethanol/day)	Smoking	Alcohol None and light		Heavy		Tobacco-specific and crude RR for alcohol consumption. Risk of drinking above median is explained almost totally by association of heavy drinking with heavy smoking. The residual effect among light (1.5) and among heavy (1.2) smokers seems compatible with residual confounding.
			None and light	1.0		1.5 (0.4-5.2)		
			Heavy	10.6 (1.6-24.1)		12.4 (5.4-28.4)		
			All	1.0		2.1 (1.1-3.9)		

[a] *, significant

(j) *Cancer of the urinary bladder*

(i) *Cohort studies* (descriptions of studies of cancers at many sites are given on pp. 158-164)

Cohort studies on mortality according to alcohol consumption which mention bladder cancer deaths are summarized in Table 71. In the prospective Japanese study (Hirayama, 1979), analysis of 77 deaths from bladder cancer in men showed no significant difference in the SMRs for daily drinkers and nondrinkers among daily smokers. In the study of Danish brewery workers (Jensen, 1980), the risk for bladder cancer was not elevated. In two small studies (Pell & D'Alonzo, 1973; Robinette *et al.*, 1979), the numbers of observed and expected cases of bladder cancer were one and 0 and none and 3, respectively.

Table 71. Relative risks (RR) for bladder cancer in cohort studies

Study and reference	No. of subjects	Results and comments		
USA, one company (Pell & D'Alonzo, 1973)	1 death	None among one-to-one matched controls not known to be alcoholic		
Finnish Alcoholics (Hakulinen et al., 1974)	5 cases	3.2 expected; RR, 1.6 (urinary organs)		
Massachussets Alcoholics (Monson & Lyon, 1975)	4 deaths	3.9 expected; RR, 1.0 (bladder and other urinary organs)		
Japanese Prospective Study (Hirayama, 1979)	77 deaths	Drinking	Smoking	RR
		daily	daily	1.4
		occasionally	daily	1.6
		no	daily	1.4
		no	no	1.0
		No. of subjects and significance not stated		
US Veterans Alcoholics (Robinette et al., 1979)	0	Three expected		
Danish Brewery Workers (Jensen, 1980)	75 cases	86.7 expected; RR, 0.9 (95% confidence interval, 0.7-1.1)		

In four further cohort studies, no distinction was made between deaths from cancer of the bladder and other parts of the urinary tract and death from other genitourinary cancers. In the study of Hawaiian Japanese (Blackwelder *et al.*, 1980), ten subjects who had died from prostatic or urinary tract cancer had had a higher unadjusted mean ethanol consumption (26.7 ml (21 g) per day) than survivors (13.6 ml (11 g) per day). A further follow-up of the same cohort showed no excess of prostatic or urinary bladder cancer

(Pollack *et al.*, 1984), but the data were not adjusted for age or tobacco use. In the Kaiser-Permanente study (Klatsky *et al.*, 1981), the distribution of 22 deaths from genitourinary cancer (ICD-8 180-189) among nondrinkers and drinkers of one to two, three to five and six or more drinks per day suggested no association. In the study of chronic alcoholics in Helsinki (Hakulinen *et al.*, 1974), five incident cases of cancers of urinary organs except prostate were observed, with 3.2 expected. In the study of Massachussets alcoholics (Monson & Lyon, 1975), four cases of cancer of the bladder and other urinary organs were observed; 3.9 were expected.

(ii) *Case-control studies*

Data from studies in which the association between alcohol consumption and bladder cancer risk was considered are shown in Table 72.

In the hospital-based case-control study in Paris, France (Schwartz *et al.*, 1957, 1962; see description, p. 167), the average daily ethanol consumption of the 214 cases (113 ml (89 g) per day) was not different from that of the accident controls (120 ml (95 g) per day) or of the cancer controls (113 ml (89 g)/day).

In a hospital-based case-control study in New York, USA (Wynder *et al.*, 1963b) of 200 male bladder cancer patients and an equal number of age-matched hospital controls (excluding patients with respiratory or upper gastrointestinal cancer or myocardial infarction), no association was detected between bladder cancer and the number of drinks consumed per day. [The Working Group noted that smoking was not controlled for.]

Dunham *et al.* (1968) interviewed 493 patients with bladder cancer (98.8% histologically confirmed) and 527 controls (mostly patients with diseases other than of the urinary tract and other than cancer) in New Orleans, USA, about factors that might have influenced their diseases (e.g., use of alcoholic beverages). No consistently positive or negative correlation with the use of alcoholic beverages was detected. [The Working Group noted the incomplete reporting of the results, and the lack of statistical evaluation and adjustment for smoking.]

In a case-control study in Canada (Morgan & Jain, 1974), 74 female and 155 male incident cases of histologically verified transitional-cell carcinoma of the bladder were compared with individually age- and sex-matched controls with benign prostatic hypertrophy (158 men) or stress incontinence (73 women). Alcohol use and smoking habits were analysed by a postal questionnaire comprising a seven-day diary of all fluid intake. Alcohol intake (ever/never) was not significantly related to cancer incidence when stratification by smoking habits (ever/never) was performed. A crude odds ratio of 1.2 fell to 1.1 after adjustment for tobacco use and sex, as calculated by the Working Group.

In the patient interview study of Williams and Horm (1977; see description pp. 170-171), no association was detected between consumption of beer, wine or spirits or total ethanol consumption and bladder cancer. The analysis was based on 229 male and 77 female cases not controlled for smoking, and 206 and 73 cases controlled for smoking. After controlling for tobacco use, the association becomes negative, especially among women. A nonsignificant positive trend with high-level beer consumption in men disappears when tobacco use is taken into account.

Table 72. Summary of results of case-control studies of bladder cancer and alcohol intake

Place (reference)	Subjects (cases, controls)	Alcohol consumption	Results[a]	Comments
USA, New York (Wynder et al., 1963b)	Men (200, 200)	No. of drinks		Crude RR and 95% CI calculated by the Working Group
		<1/month	1.0	
		1/month-6/week	1.1 (0.6-2.0)	
		1-2/day	0.9 (0.5-1.7)	
		3-6/day	1.2 (0.6-2.4)	
		7-12/day	2.1 (0.8-5.6)	
		12+	0.7 (0.2-2.7)	
		Sporadic binges	0.8 (0.3-2.4)	
USA, New Orleans (Dunham et al., 1968)	Men, women (493, 527)	Present or past occasional, light, moderate or heavy drinking		Data not shown; no consistently positive or negative association
Canada, Toronto (Morgan & Jain, 1974)	Men, women (229, 231)	Users versus non-users	1.2 (0.8-1.7) 1.1 (0.7-1.6) after adjustment for tobacco use (yes/no) and sex	Crude RR and 95% CI calculated by the Working Group
USA, Multicenter (Williams & Horm, 1977)	Men (229, 2102) Men, smoking controlled for (206, 1788) Women (77, 3464) Women, smoking controlled for (73, 3188)	Two cumulative lifetime drinking categories versus non-drinkers (at least one serving at least once a week for one year)	A nonsignificant positive trend with high-level beer consumption in men (RR, 1.4) disappears when tobacco is taken into account (RR, 1.1)	
Denmark (Mommsen et al., 1982)	Men (165, 165)	Users versus non-users	2.5 (1.0-6.3) 1.6 after adjustment for smoking (yes/no) and other variables	Crude RR

Table 72 (contd)

Place (reference)	Subjects (cases, controls)	Alcohol consumption	Results[a]		Comments
USA, ten areas	Men, women	Servings/week	Men	Women	Adjusted RR
(Thomas *et al.*, 1983)	(2982, 3313)	0	1.0	1.0	
		<3	0.9	0.8	
		4–6	0.9	0.9	
		7–13	1.0	0.8	
		14–17	0.9	1.0	
		28–41	1.1	0.9	
		≥42	1.0	0.7	
Federal Republic of Germany	Men	Beer (l/day)	Men	Women	No evidence of effect among nonsmokers
(Claude *et al.*, 1986)	(340, 340)	0.1–0.5	1.2	1.4	
	Women	0.6–1.0	2.1*		
	(91, 91)	>1	2.8*		
		Wine (l/day)			
		0.1–0.3	1.0	1.9	
		>0.3	0.8		
		Spirits (l/week)			
		0.1–0.5	1.5	1.2	
		>0.5	2.7*		
USA, Missouri	Men	Never	1.0		Adjusted RR
(Brownson *et al.*, 1987)	(846, 2536)	Ex	0.9 (0.5–1.5)		
		Current <2 drinks/day	1.2 (0.9–1.5)		
		Current ≥2 drinks/day	0.8 (0.6–1.1)		

[a]Relative risk (RR) and 95% confidence interval (CI); *, significant

In a population-based case-control study in Denmark (Mommsen *et al.*, 1982), 165 incident male cases of bladder cancer (91.5% invasive bladder cancer) and an equal number of age-, sex-and geographical area-adjusted controls were interviewed by telephone. Alcohol consumption was related to cancer incidence (crude odds ratio, 2.5; not significant). In a multivariate logistic analysis, the effect of alcohol after adjustment for cigarette smoking (yes/no), prostatic symptoms and occupation was reduced to 1.6.

In a population-based case-control study in ten areas of the USA (Thomas *et al.*, 1983), 2982 incident cases of histologically confirmed bladder cancer and 3313 general population controls were interviewed. Cases were 73% of eligible incident cases from cancer registries; controls were 82% of those identified through random selection from census fields and through random-digit telephone dialing. Alcohol consumption was estimated separately for beer, wine and spirits as the number of servings (a can, bottle or draught of beer, a 118-ml glass of wine or a 44-ml jigger of spirits) consumed during a typical week in the previous winter. After adjustment for potential confounding factors (age, sex, race, geographical location, cigarette smoking status, hazardous occupational exposure), no association between total ethanol consumption (odds ratio, 0.7-1.1) or consumption of wine, beer or spirits (odds ratio, 0.6-1.2) and bladder cancer was detected.

In a case-control study in northern Federal Republic of Germany (Claude *et al.*, 1986), 340 male and 91 female patients with histologically proven tumours of the lower urinary tract and the same number of age- and sex-matched hospital or local controls with no tumour, mainly from urological departments, were interviewed directly about consumption of different alcoholic beverages. After adjustment for smoking (lifetime cifarette consumption), beer drinkers had an overall increased RR and a clear dose-response relationship with daily intake. Drinkers of spirits also had an elevated odds ratio [1.9], while no association was found with drinking of wine. No increased risk was seen for nonsmokers who drank beer and spirits. In a multiple regression analysis, after adjustment for high-risk occupation, the risk for consumption of beer and spirits was substantially reduced and was no longer significant after adjustment for daily fluid intake. [The Working Group noted that beer and spirits were included in fluid intake and the adjustment may thus have erroneously biased the estimate of RR towards 1.]

In a case-control study based on patients registered by the Missouri Cancer Registry (Brownson *et al.*, 1987), 823 histologically verified incident cases of bladder cancer in white men were compared with 2469 cases of cancer unrelated to tobacco use (three controls per case, frequency-matched by age groups; 40% prostatic cancer and 33.5% cancers of the digestive organs and peritoneum). [The Working Group noted that the distribution of cases and controls by alcohol consumption, on which the RRs were computed, included a larger number of subjects than stated in the description of sources: 846 cases and 2536 controls with known alcohol use plus 216 cases and 596 controls with unknown alcohol use.] Information on alcohol and tobacco consumption and main occupation is systematically reported to the Registry by Missouri hospitals using a standardized protocol. No association with alcohol consumption was found, whether controlling for tobacco use and age or not. The age- and tobacco-adjusted RRs for ex-drinkers and for current drinkers (*versus* nondrinkers) were 0.9 and 1.1, respectively. Exclusion of cases of colon and rectal cancers from among the controls did not change the results.

(*k*) *Cancers at other sites*

(i) *Soft tissue*

Data on malignant tumours of soft tissue (ICD 171) are provided in the study of Danish brewery workers (based on eight observed incident cases), which shows a RR of 1.2 [95% CI, 0.52-2.36] for the whole cohort (Jensen, 1980; see pp. 162-163), and in the study of Williams and Horm (1977; see pp. 170-171), based on 45 male and 39 female cases, which shows no association.

(ii) *Skin*

In the study of Danish brewery workers (Jensen, 1980; see pp. 162-163), 77 cases of epithelial skin cancer (ICD 173) were observed with 101.9 expected (SIR, 0.8; 95% CI, 0.6-0.9). In the same study, 15 cases of melanoma were observed (SIR, 1.3; 95% CI, 0.7-2.1). In the study of chronic alcoholics in Helsinki (Hakulinen *et al.*, 1974; see p. 159), five cases of skin cancer (including basal-cell carcinoma) were observed with 6.6 expected.

In the case-control study in France (Schwartz *et al.*, 1962; see p. 167), the average ethanol consumption (129 ml (112 g)/day) of 154 patients with skin cancer (not otherwise specified) was very close to that of accident controls (139 ml; 110 g) and of cancer controls (113 ml; 89 g).

The interview study of Williams and Horm (1977; see pp. 170-171) suggested an association of melanoma with moderate alcohol consumption in men but not in women and not for higher consumption levels. The analysis was based on 40 male and 59 female cases of melanoma.

(iii) *Ovary*

The association between ovarian cancer and alcohol consumption has been considered in four case-control studies.

A study of 92 cases of ovarian malignancies and 92 cases of benign ovarian tumours in the USA, matched for age, residence and date of surgery, showed no significant difference between alcohol users and nonusers (West, 1966). [The Working Group noted that the actual figures are not given.]

The patient interview study of the Third National Cancer Survey (Williams & Horm, 1977; see description pp. 170-171), based on 180 cases and 3367 controls with cancers unrelated to tobacco use, provides a nonsignificant RR of 0.9 (not controlled for smoking) for both drinkers of 1-50 and 51 or more oz-years of ethanol, with reference to nondrinkers. For 153 cases of ovarian cancer in which smoking was controlled, the RRs were even lower.

A hospital-based case-control study at the Roswell Park Memorial Institute, USA, of 274 epithelial carcinomas of the ovary in white women aged 30-79 years and of 1034 controls (excluding cancer, gastrointestinal and endocrine disease) showed no association with alcohol consumption for women over 49 years of age (RR, 0.8-1.1). There was, however, a nonsignificant decreasing trend with increasing consumption (RR, 0.84 for one to eight drinks/week and 0.56 for nine or more) for women 30-49 years old (Byers *et al.*, 1983).

In the USA, a population-based case-control study of ovarian cancer in women under 55 years of age based on 433 incident cases (71% of total incidence) and 2915 controls (83% of potential controls selected through random-digit telephone dialing) showed a significantly lower risk (0.5; 93% CI 0.2-0.9) for 'heavy' users (250 g ethanol per week or more), especially among younger women. The estimates were adjusted for age, smoking, education, reproductive factors and oral contraceptive use (Gwinn *et al.*, 1986).

(iv) *Other organs of the female genital tract*

In the study of Canadian alcoholics (Schmidt & de Lint, 1972; see p. 164), five deaths from cancer of the uterus (not otherwise specified) were observed, with 1.4 expected. In the study of UK alcoholics (Adelstein & White, 1976; see p. 159), four deaths from cervical cancer were observed, with 0.9 expected.

The study of Williams and Horm (1977; see description pp. 170-171) showed no evidence of an association for cancers of the cervix, uterine corpus and vulva (based on 249, 345 and 30 cases, respectively, adjusted for age, race and tobacco use). The estimated RRs for both cervical and uterine corpus cancers were slightly lower than 1.0.

A study of 257 pairs of cervical cancer patients and controls (23-86 years old) in Lesotho, South Africa, showed a three-fold elevated risk among women who consumed indigenous alcohol and a two-fold risk for women who drank European alcoholic beverages after adjustment for tobacco use and other beverages (Martin & Hill, 1984).

[The Working Group noted that no adjustment for social and sexual variables was attempted in these studies.]

(v) *Prostate*

In the study of Norwegian alcoholics (Sundby, 1967; see pp. 158-159), 16 deaths from prostatic cancer were observed while 11.4 were expected on the basis of mortality in Oslo. Three deaths from prostatic cancer were observed in the follow-up of 922 alcoholics employed by a US company and none among matched controls (Pell & D'Alonzo, 1973; see p. 210). One case of prostatic cancer, with 2.8 expected, was observed among chronic alcoholics in Helsinki (Hakulinen *et al.*, 1974; see p. 159), and three cases, with 2.4 expected, were observed in the study of UK alcoholics (Adelstein & White, 1976; see p. 159).

In the Japanese prospective study (Hirayama, 1979; see p. 162), 63 deaths from prostatic cancer were reported; the SMR for daily drinking and daily smoking, as compared with nonsmokers and men who did not drink daily was 1.0 and 0.90 for daily smoking only. [The Working Group noted that the actual figures were not given.]

In the study of alcoholic US veterans (Robinette *et al.*, 1979; see p. 163), two deaths from prostatic cancer were observed, corresponding to a SMR of 0.55 (90% CI, 0.07-2.93). In the cohort of Danish brewery workers (Jensen, 1980; see pp. 162-163), 80 incident cases of prostatic cancer were observed, with 81.1 expected (SIR, 1.0; 95% CI, 0.8-1.2) in the total cohort. In the study of Canadian alcoholics, 11 deaths were seen; the SMR was 1.09 with reference to the Ontario population, and 1.43 with reference to US veterans who smoked 21-39 cigarettes/day (Schmidt & Popham, 1981).

The study of Hawaiian Japanese (Pollack *et al.*, 1984; see p. 163) provides age- and smoking-adjusted incidence rates according to amount of ethanol consumed, based on 84 incident cases of prostatic cancer. These suggest no evidence of a trend with increasing consumption.

In the case-control study of alcohol and cancer in France (Schwartz *et al.*, 1962; see description p. 167), the average consumption of 139 patients with prostatic cancer (110 ml (87 g) ethanol/day) was similar to that of controls (113 ml (89 g)).

A hospital-based case-control study in New York City of 217 patients with clinical cancer of the prostate and 200 controls with no known disease of the prostate showed no difference in alcohol consumption between the two groups (77% and 81%, respectively, were alcohol drinkers). Alcohol consumption was categorized into 1-2, 3-6, 7 or more units/day or binge, where a unit is 1 oz spirits, 4 oz wine or 8 oz beer (Wynder *et al.*, 1971).

In the study of Keller (1977; see p. 239), the age-adjusted relative frequency of prostatic cancer was slightly lower among cirrhotics. [The Working Group noted that when cases of cancer of the upper respiratory and digestive organs were excluded from the controls, the proportion of prostatic cancer among cirrhotics was slightly higher (16.7%) than among noncirrhotics (13.7%).]

In the study of Williams and Horm (1977; see pp. 170-171), of 531 cases of prostatic cancer and 1656 controls with cancer not related to tobacco use, the age- and race-adjusted odds ratios for consuming 1-50 and ≥51 oz-years of ethanol were, respectively, 0.78 and 0.84. Controlling for tobacco (465 cases and 1323 controls) did not change the estimate (odds ratios, 0.78 and 0.87).

(vi) *Testis*

Cohort studies provide no evidence that alcohol drinking in adult life affects testicular cancer incidence. The study of Danish brewery workers (Jenson, 1980; see pp. 162-163) shows a RR of 0.7 (95% CI, 0.4-1.1), based on 15 observed incident cases. In the study of alcoholic US veterans (Robinette *et al.*, 1979; see p. 163), no death from testicular cancer was observed, but there were two in the one-to-one matched comparison group.

In the hospital-based case-control study in Paris (Schwartz *et al.*, 1962; see p. 167), the average ethanol consumption reported by 37 patients with testicular cancer (112 ml (88 g)/day) was very close to that reported by the cancer control group (113 ml (89 g)) and lower than that of the accident controls (139 ml (110 g)).

In a case-control study of prenatal and perinatal factors for testicular cancer (Brown *et al.*, 1986), the alcohol consumption of the mothers of 202 cases was compared with that of 206 cases of other cancers as controls. Mothers were interviewed, and 20.3% reported consuming one to 14 drinks of alcoholic beverages per week, with a median of one drink. The crude RR (1.6; 95% CI, 1.0-2.7) for maternal alcohol consumption was confounded by smoking. No clear dose-response relationship was seen: the RR was 2.3 (1.0-5.2) for more than one drink per week and 1.1 (0.6-2.2) for one drink per week. The association was no longer significant when smoking and birth weight were taken into account in multivariate analyses.

(vii) *Kidney*

Two deaths from kidney cancer were observed in alcoholics and one in matched nonalcoholics in the cohort study of US company (Pell & D'Alonzo, 1973; see p. 210). One death from cancer of the 'kidney, ureter or other' was observed in the study of alcoholic US veterans, and four were seen in the comparison group (Robinette *et al.*, 1979; see p. 163).

In the Japanese prospective study (Hirayama, 1979; see p. 162), the SMR for kidney cancer was 1.4 for daily drinking and daily smoking and 1.4 for daily smokers only, compared with subjects who did not smoke and did not drink daily. [The Working Group noted that the actual number of cases was not given.]

In the study of Danish brewery workers (Jensen, 1980; see pp. 162-163), the RR for kidney cancer was 1.0 (95% CI, 0.7-1.4), based on 38 incident cases in the total cohort.

In the study of Schwartz *et al.* (1962; see p. 167), the average ethanol consumption of 69 kidney cancer cases (108 ml (85 g)/day) was similar to that of cancer controls (113 ml (89 g)). Accident controls consumed an average of 126 ml (99 g)/day .

The study of Williams and Horm (1977; see pp. 170-171) showed no association with alcohol consumption in either the 73 male or 53 female cases.

(viii) *Brain*

No death from brain cancer was seen in alcoholics but one in nonalcoholic controls in the study of Pell and D'Alonzo (1973; see p. 210). Among chronic alcoholics in Helsinki (Hakulinen *et al.*, 1974; see p. 159), two cases of cancer of the nervous system were observed when 1.9 were expected. The Japanese prospective study (Hirayama, 1979; see p. 162) suggested no effect of alcohol on brain cancer mortality: SMR, 1.2 for daily smoking and daily drinking, 1.5 for daily smoking and occasional drinking and 1.1 for daily smoking only.

A significant excess of brain tumours (five observed deaths against none in matched control patients with nasopharyngitis) was observed in the study of alcoholics among US veterans (Robinette *et al.*, 1979; see p. 163).

Among Danish brewery workers (Jensen, 1980; see pp. 162-163), the RR for brain and nervous system cancers, based on 37 incident cases, was 1.1 (95% CI, 0.8-1.5).

The study of Williams and Horm (1977; see pp. 170-171) compared 75 male and 61 female cases of cancer of the nervous system with cases of cancer unrelated to tobacco use. A significant negative association for the highest category of total ethanol consumption (RR, 0.4) was observed for men only.

(ix) *Thyroid cancer*

In the study of chronic alcoholics in Helsinki (Hakulinen *et al.*, 1974; see p. 159), one case of thyroid cancer was observed with 0.4 expected.

Among men in the study of Williams and Horm (1977; see pp. 170-171), there was a positive trend, with RRs of 1.1 and 1.7 for the two categories of total ethanol consumption when not controlled for smoking (based on five and nine cases, respectively). Among women, the corresponding figures were 1.6 (based on 18 cases) and 0.6 (based on two cases). The analysis comprised 30 men and 86 women with thyroid tumours.

(x) *Lymphatic and haematopoietic system*

One case of lymphoma and one of leukaemia were observed in the study of chronic alcoholics in Helsinki (Hakulinen *et al.*, 1974; see p. 159), with 1.7 and 1.2 expected, respectively.

The study of Williams and Horm (1977; see pp. 170-171) suggested that subjects with low alcohol consumption may have a lower risk of lymphosarcomas or Hodgkin's disease and a higher risk for leukaemias with respect to nondrinkers; the differences were not statistically significant, however, and there was no difference for subjects in the highest consumption category.

The study of alcoholic US veterans showed a SMR of 0.9 (based on 13 observed deaths) for lymphatic and haematopoietic cancers and a SMR of 0.5 (based on three observed cases) for leukaemia (Robinette *et al.*, 1979; see p. 163).

In the Hawaiian Japanese prospective study (Blackwelder *et al.*, 1980; see p. 163), 13 subjects died from cancer of the lymphatic and haematopoietic tissues in eight years. Their mean ethanol consumption (43.9 ml (35 g)/day) was higher than that of survivors (13.6 ml (11 g)/day). These figures are not, however, adjusted for age.

The study of Danish brewery workers (Jensen, 1980; see pp. 162-163) showed a SIR of 1.0 (based on 68 observed incident cases; 95% CI, 0.8-1.3) for lymphatic and haematopoietic cancers in the total cohort.

In the study of Keller (1977; see p. 239), the age-adjusted relative frequency of cancers of lymphatic and haematopoietic tissues was lower among cirrhotics both before and after exclusion of patients with alcohol-related cancers from among the controls.

6. SUMMARY OF DATA REPORTED AND EVALUATION

6.1 Chemical composition, consumption and trends

Alcoholic beverages are produced from raw materials by fermentation. The predominant types of commercially produced alcoholic beverages are beer, wine and spirits. The main components of all alcoholic beverages are ethanol and water; beers also contain substantial amounts of carbohydrates. Many compounds that have been identified as common to all alcoholic beverages are present in different quantities depending on the beverage. Some components and occasional contaminants include known and suspected carcinogens. Beers and wines also contain vitamins and other nutrients which are usually absent from distilled spirits. Despite the differences in concentration, the average intake of ethanol per drink is approximately constant across beverage types.

Alcoholic beverages, both home-made and commercially produced, have long been consumed in most parts of the world. Recorded consumption tends to be higher in societies with populations of European origin and lower in Muslim societies. In most of the developed countries, a majority of adults consume alcoholic beverages at least occasionally.

Since 1950, consumption per head has increased substantially in most parts of the world, although since the mid-1970s a reduction in the rate of increase and, in some countries, a decline in consumption have occurred. Drinking patterns — overall level of alcohol consumption, choice of alcoholic beverages, differences by sex and age and temporal variations — differ among and within societies.

6.2 Experimental carcinogenicity data

Ethanol and some alcoholic beverages were tested for carcinogenicity in five studies in mice by oral administration. Ethanol was also tested in one experiment by transplacental exposure or exposure *via* mother's milk. Due to severe limitations in experimental design or conduct, these studies could not be used for an evaluation of carcinogenicity.

Two studies involved oral administration of ethanol and of one alcoholic beverage to rats. One study was inadequate for evaluation, and in the other no difference in the incidence of tumours was found.

In seven studies, ethanol or an alcoholic beverage was administered to rats as a control in studies of combined effects with a known carcinogen. In one of these, involving male animals only, ethanol administered in water as the drinking fluid significantly increased the incidences of hepatocellular carcinomas and of tumours of the pituitary gland, of the adrenal gland and of pancreatic islet cells, but neither isocaloric nor isonutrient diets were used. All of these studies, however, suffered from various limitations and could not be used for evaluation.

Ethanol and certain alcoholic beverages were administered to hamsters by oral administration in four studies, three of which were designed to ascertain combined effects with known carcinogens. All of these studies suffered from various limitations and could not be evaluated. One study in mice involving application of ethanol or residues of alcoholic beverages to the skin could also not be evaluated.

In experiments in which various carcinogens were administered orally with ethanol as a vehicle, ethanol enhanced the incidence of nasal cavity tumours induced in mice by *N*-nitrosodimethylamine and enhanced the incidences of oesophageal/forestomach tumours and lung tumours induced in mice by *N*-nitrosodiethylamine or *N*-nitrosodi-*n*-propylamine.

In further studies, various carcinogens were administered by different routes simultaneously with ethanol in water as the drinking fluid or in liquid diets. Ethanol enhanced the incidence of benign tumours of the nasal cavity induced in rats by *N'*-nitrosonornicotine given in a liquid diet, and enhanced the incidences of nasal cavity and tracheal tumours and of neoplastic nodules of the liver induced in hamsters by *N*-nitrosopyrrolidine given by intraperitoneal injection. Administration of ethanol in the drinking-water enhanced the incidences of hepatocellular carcinomas and of liver angiosarcomas induced in rats by inhalation of vinyl chloride.

In a number of other experiments, ethanol had no modifying effect on the overall incidence of tumours in mice, rats or hamsters given *N*-nitrosomethylbenzylamine, *N*-nitrosobis(2-oxopropyl)amine, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, 7,12-dimethyl-benz[*a*]-anthracene or 1,2-dimethylhydrazine by various routes of administration.

There is *sufficient evidence* for the carcinogenicity of acetaldehyde (the major metabolite of ethanol) in experimental animals.

6.3 Human carcinogenicity data

Cancers of the oral cavity and pharynx

In six retrospective cohort studies of persons with an intake of alcoholic beverages higher than that of the reference population and including alcoholics and brewery workers, the risk for cancers of the oral cavity and pharynx (effectively excluding the nasopharynx) has been examined. In five studies of alcoholics, the relative risk was significantly increased by between two and five fold.

In two prospective cohort studies, the risk for cancers of the oral cavity, pharynx, larynx and oesophagus combined and for cancers of the oral cavity, pharynx and oesophagus combined increased with the daily number of drinks.

Case-control studies have been performed of cancers of the oral cavity (11 studies), pharynx (ten studies), and oral cavity and pharynx combined (two studies). In all but two of the studies, the risk increased significantly with increasing level of consumption of alcoholic beverages; in two studies, nonsignificant increases were observed. These results persisted after adjustment for tobacco smoking. The risk increased with daily intake of alcoholic beverages at any level of tobacco smoking in six studies in which this was examined, and the risk for cancer increased with amount drunk by nonsmokers in three out of four studies in which this aspect was examined.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to cancers of the oral cavity and pharynx (excluding the nasopharynx). There is no indication that the effect is dependent on type of beverage.

Cancer of the larynx

Data on laryngeal cancer were provided by six retrospective cohort studies — five of alcoholics and one of brewery workers. The risk for laryngeal cancer was significantly increased by two to five fold in four of the studies.

Fourteen case-control studies in North America and Europe all showed that the relative risk increased with level of intake of alcoholic beverages. Three large studies indicated that the risk associated with intake of alcoholic beverages was stronger for cancer at sites at the junction between the larynx and pharynx than for cancer of the endolarynx. These results persisted after adjustment for tobacco smoking. In nine of the studies in which this was examined, it was reported that the association with drinking of alcoholic beverages was seen at any level of smoking. Three studies have been carried out on small groups of lifetime nonsmokers; the relative risk increased with amount of drinking in one, but no difference was seen in the proportion of drinkers and nondrinkers in the two others.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to laryngeal cancer. There is no indication that the effect is dependent on type of beverage.

Cancer of the oesophagus

Seven of eight retrospective cohort studies of alcoholics and brewery workers showed two- to four-fold increased risks of cancer of the oesophagus, although this was nonsignificant in two. Of 13 case-control studies, 11 showed significantly increased relative risks with level of intake of alcoholic beverages. The increased risk persisted after adjustment for tobacco smoking and was seen at all levels of tobacco smoking in the two studies in which this was examined. The risk increased with intake of alcoholic beverages in a small number of persons who had never smoked in the only study in which this aspect was examined.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to cancer of the oesophagus. There is no indication that the effect is dependent on type of beverage.

Cancer of the stomach

In three of 13 cohort studies, stomach cancer risk was increased in association with consumption of alcoholic beverages, but in only one was this statistically significant. Summation of observed and expected numbers of cases of stomach cancer in the eight retrospective cohorts of persons with above-average consumption of alcoholic beverages indicates a slight deficit in risk.

Data have been reported from 12 case-control studies on the relationship between drinking of alcoholic beverages and stomach cancer. In two studies, the risk for stomach cancer was positively and significantly associated with consumption of alcoholic beverages. In another study, a significant increase in risk was found with one specific drinking practice. One study reported a nonsignificant reduction in the risk for stomach cancer associated with drinking of alcoholic beverages.

In most epidemiological studies of alcoholic beverages and stomach cancer, including all nine retrospective cohort studies, there was no adjustment for any possible confounding effect of diet.

In view of the overall lack of excess risk for stomach cancer in the cohort studies, the inconsistent results of the case-control studies, and the inadequate control for dietary and socioeconomic factors, there is little in the aggregate data to suggest a causal role for drinking of alcoholic beverages in stomach cancer.

Cancer of the large bowel

Two of 13 cohort studies of colon cancer showed an increase in risk, while another showed a nonsignificantly decreased risk associated with raised consumption of alcoholic beverages. Summation of observed and expected numbers of cases of colon cancer in the nine retrospective cohorts of persons with above-average consumption of alcoholic beverages indicates no overall shift in the risk.

For rectal cancer, the risk was increased in association with drinking of alcoholic beverages in four of nine cohort studies. In two of these four studies, a significant increase was seen in relation to beer consumption, including one study in which there was evidence of a dose-response relationship up to a three-fold increase in risk. In the two others, nonsignificant, two- to three-fold increases in the risk for rectal cancer in alcoholics were reported. Summation of observed and expected numbers of cases of rectal cancer in the seven retrospective cohorts of persons with above-average consumption of alcoholic beverages indicates a slight (15%) excess of cases.

Of the four cohort studies in which data were reported on colon and rectal cancers combined, one showed a significant, two-fold increase, while two others showed a nonsignificant increase in risk with raised consumption of alcoholic beverages.

In four of eight case-control studies of colon cancer, a significant positive relationship was evident with drinking of specific beverages: with beer consumption in two studies, and with spirits consumption in three studies.

In six of nine case-control studies of rectal cancer, a significant positive relationship with drinking of alcoholic beverages was reported. In three studies, beer consumption was significantly associated with rectal cancer in men only; in one study, this association was significant for men and women combined. Of the other two studies with significant positive results, one showed an association with consumption of spirits, the other with total ethanol consumption. A case-control analysis within one of the studies of brewery workers showed a positive relationship between drinking of stout and rectal cancer risk.

In most epidemiological studies of consumption of alcoholic beverages and large-bowel cancer, including all nine retrospective cohort studies, there was no adjustment for any possible confounding effect of diet.

In view of the inconsistent findings from epidemiological studies and the probability of uncontrolled confounding by dietary factors, no conclusion can be drawn about the role of consumption of alcoholic beverages in the causation of colon cancer.

Overall, some of the epidemiological studies provide suggestive but inconclusive data for a causal role of drinking of alcoholic beverages, most often beer consumption, in rectal cancer.

Cancer of the liver

Of four cohort studies of the general population, two showed a significantly increased risk for liver cancer among drinkers of alcoholic beverages, whereas in a third study an increased risk was found only among a subgroup of drinkers in one of the two populations studied. Three of ten cohort studies of persons with high intake of alcoholic beverages showed a significant association between consumption of alcoholic beverages and liver cancer, whereas in five other studies the association was positive but nonsignificant. Summation of observed and expected numbers of cases of liver cancer in these ten studies on special cohorts indicates a significant 50% increase in risk.

Six of ten case-control studies showed significant associations at the two- to three-fold level between consumption of alcoholic beverages and primary liver cancer.

A particularly strong association between consumption of alcoholic beverages and primary liver cancer was demonstrated in a cohort study of hepatitis B surface antigen-positive volunteer blood donors. The results of one case-control and one cohort study suggest that the risk for liver cancer is particularly high among people who both drink alcoholic beverages and smoke cigarettes.

Potential confounding due to hepatitis B virus, tobacco smoking and aflatoxin was not explored in all the studies; whenever it was, it did not alter the findings qualitatively. The available results, taken together, indicate that drinking of alcoholic beverages is causally related to liver cancer.

Cancer of the pancreas

Of five cohort studies of the general population, only one showed a significantly increased incidence of cancer of the pancreas among regular drinkers of alcoholic beverages; of ten cohort studies of persons with high intake, none showed a significant association between consumption of alcoholic beverages and pancreatic cancer risk. Of 14 case-control studies, only one has indicated an increased pancreatic cancer risk among regular drinkers of alcoholic beverages. Taken together, the results of these 29 studies suggest that consumption of alcoholic beverages is unlikely to be causally related to cancer of the pancreas.

Cancer of the breast

A significant positive association between intake of alcoholic beverages and breast cancer incidence was seen in each of four large prospective studies and in seven of 13 case-control studies. Nonsignificant positive associations of similar magnitude were observed in two of the case-control studies, in which there were relatively few persons. A dose-response relationship, generally with up to 1.5- to two-fold risks, has been observed. The consistency of this positive association makes it unlikely that the relationship is due to chance or methodological bias. There is no indication that the association is dependent on type of beverage.

Confounding due to currently recognized risk factors for breast cancer was controlled for in most studies; in no instance did adjustment for these factors appreciably alter the estimated risk. In view of the modest elevations in relative risks observed, the possibility of confounding by an unrecognized factor cannot be ruled out entirely, especially since much of the etiology of breast cancer remains unexplained. In order that such a factor be sufficient to explain the observed associations with the drinking of alcoholic beverages, however, it would have to be much more strongly associated with the occurrence of breast cancer than the known common risk indicators and, also, highly correlated with consumption of alcoholic beverages.

The modest elevation in relative risk that has been observed is potentially important because of the high incidence of breast cancer in many countries. Although the available data indicate a positive association between drinking of alcoholic beverages and breast cancer in women, a firm conclusion about a causal relationship cannot be made at present.

Cancer of the lung

Fifteen cohort studies of alcoholics, of persons with higher than average consumption of alcoholic beverages and of the general population have yielded inconsistent results on an association between drinking of alcoholic beverages and the risk for lung cancer. Smoking was taken into account in only five of these studies. In five case-control studies, there was no association between risk for lung cancer and consumption of alcoholic beverages. In view of the lack of excess risk in case-control studies and the inconsistent results of cohort studies, there is no indication that drinking of alcoholic beverages has a causal role in lung cancer.

Cancers at other sites

Overall, studies on cancers of the urinary bladder, kidney, ovary, prostate and lymphatic and haematopoietic system show no association with consumption of alcoholic beverages. The sparsity of the observations on cancers of the skin, corpus and cervix uteri, vulva, testis, brain, thyroid and soft tissues precludes an evaluation.

6.4 Other relevant data

Toxic effects and metabolism

The concentrations of ethanol attained in humans in the upper gastrointestinal tract after consumption of alcoholic beverages can cause local irritation. Long-term, excessive drinking of alcoholic beverages can also cause fatty liver, alcoholic hepatitis, cell necrosis, fibrosis and cirrhosis in the liver.

In humans and experimental animals, ethanol metabolism generates acetaldehyde, predominantly in the liver, and low concentrations of acetaldehyde are found in the blood. In alcoholics, the rate of ethanol oxidation is enhanced, resulting in increased levels of acetaldehyde in the liver and blood. In some ethnic groups, the absence of a specific form of aldehyde dehydrogenase leads to elevated acetaldehyde concentrations in tissues and blood after ingestion of alcohol.

An acute effect of ethanol is inhibition of the metabolism of xenobiotics in humans and experimental systems. In rodents, administration of nitrosamines together with ethanol results in increased DNA alkylation in some extrahepatic tissues such as oesophagus and kidney. Long-term ingestion of ethanol by humans and experimental animals increases levels of cytochrome P450 in the liver, resulting in enhanced metabolism of a wide variety of xenobiotics.

Alterations in hormonal status have been described after either acute or chronic ingestion of ethanol in some studies in humans and experimental animals.

Effects on reproduction

In humans, ethanol is a developmental toxin, and various effects have been associated with ethanol intake. Excessive consumption of alcoholic beverages during pregnancy is associated with the development of a syndrome of physical and mental manifestations in the offspring — the fetal alcohol syndrome; it may also cause defects in the central nervous system, heart, kidney and limbs. Moderate consumption can be associated with reduced birth weight and behavioural deficits, but effects generally have not been observed with an intake of about one drink per day.

Ethanol at high blood levels affects the structure of the reproductive organs and causes significant reductions in fetal body weight, increased resorptions and teratogenic effects in a number of species. Behavioural development of mice and rats was affected by exposure to ethanol *in utero* in some, but not all, studies; exposure *in utero* or during lactation reduced postnatal growth.

Ethanol crosses the placenta in a variety of species, and both ethanol and acetaldehyde have been found in fetal tissues after dosage of pregnant rodents with ethanol. Both ethanol and acetaldehyde can cause embryonal developmental abnormalities *in vitro*.

Genetic and related effects

Increased frequencies of chromosomal aberrations, sister chromatid exchanges and aneuploidies were found in the peripheral lymphocytes of alcoholics.

In rodents exposed *in vivo*, ethanol induced dominant lethal mutations in mice and rats and aneuploidy in germ cells of mice, but did not induce chromosomal aberrations in rats or Chinese hamsters. It induced sister chromatid exchanges in mice and rats but not in Chinese hamsters. It did not induce micronuclei in mice, but conflicting results were obtained in rats. It induced sister chromatid exchanges in mouse embryos exposed *in vivo* and, in one study, chromosomal aberrations in rat embryos exposed *in vivo*.

In most studies of human cells *in vitro*, ethanol did not induce chromosomal aberrations in the absence of an exogenous metabolic system or sister chromatid exchanges in the presence or absence of an exogenous metabolic system. In limited studies, ethanol gave positive results in tests for morphological cell transformation in mouse C3H 10T1/2 cells but not in Syrian hamster embryo cells. In rodent cells *in vitro*, sister chromatid exchanges were induced in the presence, but generally not in the absence, of an exogenous metabolic system. Neither micronuclei nor chromosomal aberrations were induced in the absence of an exogenous metabolic system. Ethanol did not induce DNA damage or mutation in rodent cells *in vitro*. It did not induce mutation or recombination in *Drosophila*.

In plant roots, ethanol induced chromosomal aberrations and sister chromatid exchanges and, in one study, micronuclei in tetrads. In fungi, it induced mutations and nondisjunction; in single studies, it induced mitotic crossing-over but not gene conversion. Ethanol did not induce mutation or DNA damage in bacteria.

Ethanol-free extracts of some alcoholic beverages induced sister chromatid exchanges in human cells *in vitro* and mutation in bacteria.

6.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of ethanol and of alcoholic beverages in experimental animals.

There is *sufficient evidence* for the carcinogenicity of alcoholic beverages in humans.

[1]For definition of the italicized terms, see Preamble pp. 27-30.

The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver is causally related to the consumption of alcoholic beverages.

Alcoholic beverages *are carcinogenic to humans* (Group 1).

APPENDIX C

REPORT ON CARCINOGENS (RoC), 9th EDITION
REVIEW SUMMARY

Report on Carcinogens (RoC), 9th Edition
Review Summary

Alcoholic Beverage Consumption

NOMINATION
Review based on letter from Dr. Hiroshi Yamasaki (IARC) recommending listing in the RoC based on IARC classification of Alcoholic Beverage Consumption as a known human carcinogen (IARC Vol. 44, 1988).

DISCUSSION
Alcoholic Beverage Consumption is causally related to cancers of the mouth, pharynx, larynx, and esophagus and may be causally related with cancers of the liver and breast. Studies indicate that the risk is most pronounced among smokers and at the highest levels of consumption. There is possible confounding of epidemiology studies by smoking, diet, and poor oral hygiene. However, these factors cannot account for the observed causal association between alcoholic beverage consumption and cancer. The effects of alcohol and smoking may be synergistic, which would put smokers at the highest risk for cancer development. Possible beneficial cardiovascular effects of low to moderate consumption of alcoholic beverages have been reported. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known human carcinogen	6 yes/1 no
NTP EC Working Group (RG2)	list as known human carcinogen	7 yes/0 no
NTP Board RoC Subcommittee	list as known human carcinogen	9 yes/3 no/1 a*

*a-abstentions

Public Comments Received
A total of 19 public comments were received:

- 2 in favor of listing as a known to be human carcinogen
- 15 against listing in the RoC in any category
- 2 providing comments on the content of the background document prepared for the review of this nomination

CHAPTER

19

Alcohol and Cancer

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OVERVIEW

Alcoholic beverage consumption causes cancer of the mouth, pharynx, larynx, esophagus, and liver. It is likely that alcohol also causes pancreatic cancer, but this outcome is so rare that epidemiologic data cannot detect the relation. Alcohol is clearly associated with increased risk of breast cancer, and it is primarily lack of an established mechanism that precludes conclusions regarding causality. Alcohol is also associated with risk of colorectal cancer, although the epidemiologic data are somewhat less convincing than for breast cancer. The lack of consistent association between alcohol and risk of endometrial cancer suggests that alcohol's effect on carcinogenesis is not via estrogens. Although data suggest an association between alcohol and lung cancer, the possibility that this is due to residual confounding by smoking precludes interpretation of the association as casual.

The mechanism by which alcoholic beverage consumption causes human cancer is not established,although support is increasing for at least some of the risk being due to alcohol's metabolism to acetaldehyde, an established carcinogen in animal models.

Overall, the consistent presence of the dose–response relation for many sites suggests that risk is proportional to dose, even at light and moderate intakes. The proportion of cancers attributable to alcohol consumption is less than 2%. The potential cancer risk associated with alcohol consumption should be balanced against other health effects of alcohol, including the benefits for cardiovascular disease. A reasonable public health message is that if you choose to drink, do not drink too much.

INTRODUCTION

Natural Exposure

The production of ethanol by endogenous human flora results in blood level of 0.1–0.5 mg/dl (Jones, 1994). Compared with the 80–100 mg/dl defining legal intoxication in the United States (Hingson *et al.*, 1994), however, these levels are minuscule. Ethanol can occur in high concentrations in overripe fruit (Mallon and Katelaris, 1997), and gorging on overripe apples has reportedly led to intoxication in bears (McPhee, 1985). Intermittent human exposure to relatively high doses of naturally-occurring ethanol has probably been ongoing for millennia.

Ethanol Metabolism

The pathways involved in human ethanol metabolism are shown in Fig. 19.1. Genetic polymorphisms that affect ethanol metabolism have been identified for cytochrome oxidase CYP 2E1, for aldehyde dehydrogenase (ALDH), and possibly for alcohol dehydrogenase type 3 (ADH3), but not type 2 (ADH2) (Iwahashi *et al.*, 1996; Mizoi *et al.*, 1994; Bosron and Li, 1986). Polymorphisms that increase acetaldehyde levels may increase cancer risk among drinkers (Yokoyama *et al.*, 1996).

Because males have more gastric ADH than do females, for a given amount of ethanol consumed, blood alcohol level tends to be greater in females (Frezza *et al.*, 1990). In addition, for a given weight, females tend to have less lean body mass into which alcohol is primarily distributed, and females tend to be smaller than males. Thus, for a given amount of alcohol con-

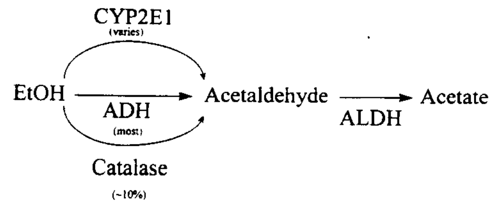

FIGURE 19.1 The pathways involved in human ethanol metabolism. EtOH, ethanol; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase. Material in parentheses indicates proportion of ethanol metabolized by that pathway.

sumed, the physiologic dose tends to be higher in females. Together, these gender differences in alcohol metabolism suggest that alcohol–cancer dose–response relations should be steeper in females for those cancer sites where the mechanism involves tissue exposure via the bloodstream. Gender-specific definitions of heavy drinking for men (>2 drinks/day) and women (>1 drink/day) have been proposed (U.S. Department of Agriculture, 1990), reflecting the differences in alcohol metabolism and the steeper slope of the dose-response curve for cirrhosis in women (Tuyns and Pequignot, 1984).

Historical Notes on the Use of Ethanol by Humans

Accumulations of grape seeds have been excavated in neolithic ruins from 8000 B.C. (Johnson, 1989). Early evidence of alcohol consumption dates from the bronze age: the estimated date of human ethanol intoxication at about the time of the great flood in the Bible (Genesis, chapter 9) is 2800 B.C. (Pelligrino, 1994). Perhaps more reliable dating derives from Hammurabi's laws concerning commerce in wine (Johnson, 1989), recorded about 1750 B.C.

Use of Alcoholic Beverages in the United States

In general, about one-third of Americans do not drink alcoholic beverages, another third drink less than half a drink a day, and the remaining third drink moderately or heavily (Hurley and Horowitz, 1990). Moderate consumption ranges from an average of half a drink/day to less than two drinks per day, while heavy consumption is an average of two drinks/day or more. About 10% of people in the United States drink heavily. Recent trends in alcohol consumption have been toward a slightly higher prevalence of abstinence and towards lighter drinking among drinkers (Midanik and Clark, 1994). On average, men drink about twice as much as women (Dawson and Archer, 1992).

The Validity of Self-Reported Alcohol Consumption

The validity of measures of alcohol consumption used in epidemiologic studies is supported by good correlations between self-reported alcoholic beverage use assessed by different methods (Giovannucci *et al.*, 1991), and by moderate correlations between self-reported intake and biologic measures affected by alcohol consumption (Linn *et al.*, 1993; Steffensen *et al.*, 1997). Despite evidence for the validity of these measures, however, alcohol intake is known to be widely underreported. According to national survey data, the average daily intake of ethanol among U.S. adults is 14 g (Dawson and Archer, 1992)—substantially less than the adult per capita intake of 21 g/day estimated from sales data (Midanik and Clark, 1994). Thus, only two-thirds of the alcohol consumed in the United States is reported (Embree and Whitehead, 1993). Because heavy drinkers are underrepresented in surveys (Cottler *et al.*, 1987), the proportion of alcohol intake reported may be slightly higher than two-thirds. Nonetheless, the implication for interpretation of epidemiologic studies is that the observed dose-response curves are about 50% steeper than they would be in the absence of systematic underreporting. The overestimation of the dose-response relation due to underreporting may be countered in part by the effect of nondifferential misclassification of alcohol consumption.

METHODS USED IN THIS REVIEW

Because numerous epidemiologic studies of alcohol and cancer have been conducted over the past 40 years, we chose to focus on the five largest studies for each site. Study size was judged by the number of cases.

Studies were identified by a search of the Medline database through September of 1997 using the WinSPIRS-Medline software (Silver Platter Software International, NV, 1995), using the keywords "alcohol" and the specific type of cancer. The electronic search results were supplemented by citations in Jensen *et al.*, (1996), Longnecker and Enger (1996), and the authors' personal knowledge.

The eligibility criteria for inclusion were (a) the study design had to be case-control or follow-up, (b) the exposure assessment method used in the study had to be the same for cases and noncases, (c) subjects had to have been divided into at least three categories of alcohol consumption, (d) units of alcohol consumption in the study had to be in terms of or convertible to grams per day of ethanol, and (e) results had to be adjusted for age, and for smoking for those cancers known to be associated with smoking: mouth, pharynx, larynx, esophagus, pancreas, lung, and endometrium. We also cited data from smaller studies in the review where needed.

Results of studies meeting the criteria for inclusion were summarized in tables. To reexpress categories of alcohol consumption in terms of grams per day of ethanol, where necessary, we assumed that one alcoholic drink contains 13 g of ethanol. To convert finding based on lifetime alcohol intake to grams per day, we assumed that alcohol consumption began at age 25 and ended the average age of cases' diagnosis; this assumption would tend to slightly overestimate the dose–response slope.

Median ethanol intake for each category of alcohol consumption reported by original authors was calculated as described elsewhere (Longnecker *et al.,* 1990). When results for males and females were reported separately in the original report, we averaged the results across gender (Greenland, 1987) before presentation in our summary tables. If original male and female results were obtained using different scales of alcohol consumption, only the results for males were shown in our table.

Within-study weighted least squares regression models were fitted to summarize the dose–response relation in each study, using the covariance adjustment method of Greenland and Longnecker (1992). Random effects models (DerSimonian and Laird, 1986) were then fitted to the slopes of the five studies for each site, in order to characterize the overall dose–response relation for each type of cancer. Dose–response relations both within and across studies were summarized as β, the change in the logarithm of the relative risk associated with each gram of alcohol consumed per day. The β coefficients can be converted to relative risks (RR) with nondrinkers as the reference group using the formula RR = $e^{\beta * g \text{ ethanol}}$. Thus, for example, the relative risk associated with consumption of three alcoholic drinks (39 g ethanol) daily is $e^{\beta * 39}$. Heterogeneity of study-specific slopes for each site was evaluated using the deviance (D), the model fit statistic from our random effects model, which has a chi-square distribution. A larger D indicates greater heterogeneity among studies, and $D > 9.49$ (4 d.f.) is statistically significant at the $\alpha = 0.05$ level.

We applied the methods described above for cancers of the mouth, pharynx, larynx, esophagus, liver, pancreas, large bowel, breast, and endometrium. For other cancers, for which we felt alcohol was less important etiologically based on the results of previous reviews and the updated literature search, we summarized the major findings in the text.

SITE-SPECIFIC RELATIONS

Oral and Pharyngeal Cancer

Slope and Heterogeneity

The dose–response relation between alcoholic beverage consumption and oral cancer is clear (Table 19.1). The overall summary slope, reexpressed as the relative risk associat-

TABLE 19.1 Relative Risk of Cancer of the Mouth According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Blot *et al.*	743	0 - 1.7	1		30.2	2.1
(1988)		1.7– 7.4	1.1	0.8– 1.6		
U.S.		9.3– 26	1.5	1.1– 2.1		
		27.9– 53.9	2.9	2.0– 4.1		
		55.8+	8.7	6.0–12.5		
Notani[b]	278	0	1		16.4	22.8
(1988)		1.9+	1.2	0.7– 1.9		
India						
Franco *et al.*	232	0 - 0.1	1		12.7	1.4
(1989)		0.1– 9.1	2.7	1.0– 7.2		
Brazil		9.2– 36.4	3.5	1.3– 9.8		
		36.5– 91	7.1	2.6–19.5		
		91.1+	8.8	4.8–16.2		
Zheng *et al.*	248	0	1		15.3	6.6
(1990)		0.1– 10.3	1.3	0.7– 2.3		
China		10.4– 19.6	1.1	0.6– 2.1		
		20 - 39.6	1.4	0.7– 2.6		
		39.7+	2.8	1.2– 6.3		
Franceschi *et al.*	157	0 - 35.2	1		8.5	2.4
(1990)		37.2– 63.2	1.1	0.5– 2.5		
Italy		65.1–109.7	3.2	1.6– 6.2		
		111.6+	3.4	1.7– 7.1		
Overall summary slope					16.8	5.2
	$D = 60$, d.f. = 4					

[a]All results are adjusted for at least age and smoking.
[b]Notani (1988) did not present results for those drinking 0.1–1.8 g/d.

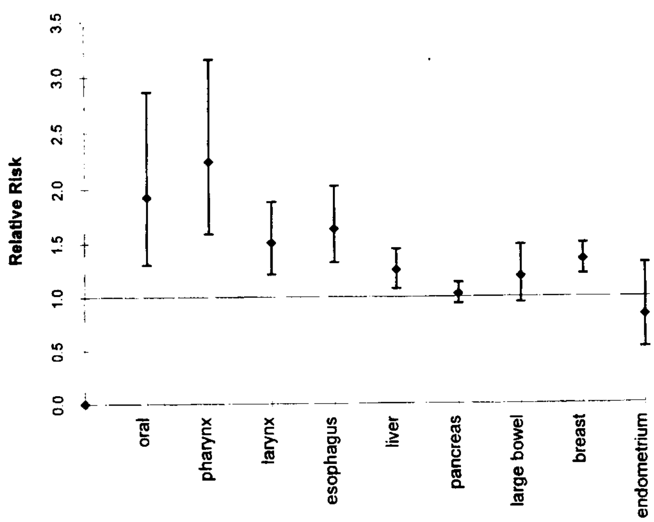

FIGURE 19.2 Estimated relative risk and 95% confidence intervals of specified cancers associated with consumption of on average three alcoholic drinks daily. Estimates are based on random effects models summarizing results of the five largest studies of each site.

ed with consumption of an average of three alcoholic drinks daily, is shown in Fig. 19.2. The strength of the association between alcohol and oral cancer, as reflected by the study-specific slopes, varies considerably. The slopes derived from studies in the United States (Blot *et al.,* 1988) and Italy (Franceschi *et al.,* 1990) differ by more than threefold. Although the Italian study in table 19.1 (Franceschi *et al.,* 1990) is positive, not all Italian studies show an association (Merletti *et al.,* 1989). The reason for the variation in association among studies may be in part due to beverage preferences in different countries (see section on Nuances, below), to different drinking patterns in different countries (steady intake vs. large amounts at once), to varying degrees of underreporting alcohol consumption across countries, or to differences in study design. Although data on alcohol and oral cancer from India often appear not to support an association (Nandakumar *et al.,* 1990; Notani, 1988), alcohol use is relatively limited in that population, rendering studies in India rather uninformative.

The comments made about slope and heterogeneity for oral cancer apply equally well to pharyngeal cancer (Table 19.2). Oral cancer and pharyngeal cancer are frequently com-

TABLE 19.2 Relative Risk of Cancer of the Pharynx According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Blot *et al.*	373	0 - 1.7	1		32.2	2.5
(1988)		1.7- 7.4	1.5	0.9- 2.4		
U.S.		9.3- 26	1.6	1.0- 2.5		
		27.9- 53.9	4.0	2.5- 6.4		
		55.8+	11.5	7.1-18.4		
Notani[b]	225	0	1		30.2	22.4
(1988)		1.9+	1.4	0.9- 2.4		
India						
Tuyns *et al.*	281	0 - 20	1		18.1	1.9
(1988)		21 - 40	1.6	0.7- 3.4		
Europe		41 - 80	3.2	1.6- 6.2		
		81 -120	5.6	2.8-11.2		
		121+	2.5	6.3-25.0		
Franceschi *et al.*	134	0 - 35.2	1		10.2	2.4
(1990)		37.2- 63.2	0.9	0.4- 2.0		
Italy		65.1-109.7	1.5	0.8- 3.1		
		111.6+	3.6	1.8- 7.2		
Choi and Kahyo	133	0	1		21.1	3.5
(1991)		0.1- 22.4	1.2	0.6- 2.5		
Korea		22.5- 45	2.2	1.1- 4.2		
		45 - 90	4.1	2.1- 7.9		
		91+	11.2	4.2-29.8		
Overall summary slope					20.7	4.5
	$D = 41$, d.f. $= 4$					

[a]All results are adjusted for at least age and smoking.
[b]Notani (1988) did not present results for those drinking 0.1–1.8 g/d.

bined in epidemiologic studies (Blot *et al., 1988; Marshall et al.*, 1992; Ng *et al.*, 1993; Mashberg *et al.*, 1993), and the similarity of the overall summary slopes shown in Tables 19.1 and 19.2 supports the appropriateness of combining the two. Among studies presenting results for both sites (Blot *et al.*, 1988; Notani, 1988; Franceschi *et al.*, 1990; Choi and Kahyo, 1991), associations of alcohol intake with oral and pharyngeal cancer are usually comparable.

Confounding and Interaction

Because alcohol intake is associated with smoking and with poor diet, both known risk factors for oropharyngeal cancer, these two factors are potential confounders of the alcohol–oral cavity association. The increased risk of oral and pharyngeal cancer among heavy drinkers persists, however, after adjusting for dietary factors such as low fruit and vegetable intake (Franceschi *et al.*, 1994; Kune *et al.*, 1993). In addition, the effect of alcohol among lifelong nonsmokers has been clearly demonstrated (Baron *et al.*, 1993; Blot *et al.*, 1988; Ng *et al.*, 1993). The effects of smoking and drinking together on risk of oral and pharyngeal cancer are more than additive (Baron *et al.*, 1993; Mashberg *et al.*, 1993; Choi and Kahyo, 1991; Blot *et al.*, 1988; Zheng *et al.*, 1990; Franco *et al.*, 1989).

Precursors, Subsites, and Histology

Whether alcohol consumption increases risk of oral leukoplakia or oral epithelial dysplasia is unclear (Morse *et al.*, 1996). Cancer of the lip and salivary glands are usually excluded from epidemiologic studies of oral cancer (e.g., see MacFarlane *et al.*, 1995). The study by Blot *et al.*, (1988) is the most informative regarding site-specific effects because of its size, and no clear difference between tongue and other oral cancers was present in those data. Franco *et al.*'s data (1989) also support no difference by subsite within the mouth. Risk of nasopharyngeal carcinoma in relation to alcohol use was examined by Armstrong *et al.*, (1983) and no association was found.

Nuances

Blot *et al.'s* (1988) data suggest that consumption of alcohol in beer and spirits increases risk of oropharyngeal cancer more than consumption of an equivalent amount of alcohol in wine. The smallest slopes in Table 19.2 were both from studies done in populations where the preferred beverage type was wine (Tuyns *et al.*, 1988; Franceschi *et al.*, 1990). Comparison among beverage-specific effects among Italians is difficult because relatively little beer and spirits are consumed. Imbalanced distribution of beverage-specific consumption within a given population frequently hampers comparisons of beverage effects within and across populations (Kabat and Wynder, 1989; Franco *et al.*, 1989). Rothman *et al.*, (1989) found that consumption of dark distilled spirits was associated with a greater risk of hypopharyngeal cancer than was consumption of light distilled spirits, conditional on total amount of alcohol consumed. This evidence was interpreted as supportive of congeners in dark distilled spirits having an independent effect on carcinogenesis at this site.

Although alcohol in mouthwash was implicated as increasing risk of oral cancer (Winn *et al.*, 1991), a recent reconsideration of the issue raises doubt regarding whether mouthwash use can be reliably disentangled from the effect of alcoholic beverages (Shapiro *et al.*, 1996).

Harty *et al.*, (1997) recently reported that subjects with a polymorphism of ADH3 that converts alcohol to acetaldehyde relatively rapidly have greater risk of alcohol-associated oral cancer.

Brennan *et al.*, (1995) reported that the prevalence of p53 mutations in persons who smoked was higher among drinkers than among nondrinkers, but did not consider amount smoked in their comparison. Field *et al.*, (1994) examined the effect of drinking after stratifying on smoking and found evidence that drinking increased p53 prevalence in cases. Other studies provide no support for alcohol consumption being associated with p53 mutations in head and neck cancer (Lazarus *et al.*, 1996; Franceschi *et al.*, 1995).

Larynx

Slope and Heterogeneity

The dose–response relation between alcoholic beverage consumption and cancer of the larynx is usually clear (Table 19.3). The overall summary estimated slope is about half that estimated for oropharyngeal cancers. Again, however, the strength of the association varies markedly—the Italian study (Franceschi *et al.*, 1994) showed essentially no increase in risk among heavy drinkers, whereas others show a 2 to 4 fold difference in risk comparing heaviest to lightest consumers of alcohol.

Confounding and Interaction

The association between alcohol intake and laryngeal cancer is not due to confounding by smoking or poor diet (Franceschi *et al.*, 1994; Graham *et al.*, 1981; Hedberg *et al.*, 1994). A study conducted in Italy (Baron *et al.*, 1993) showed a modest dose–response relation for alcohol among lifelong nonsmokers. Alcohol intake and smoking interact; together their effect on risk of laryngeal cancer is more than additive (Choi and Kahyo, 1991; Tuyns *et al.*, 1988; Franceschi *et al.*, 1990; Freudenheim *et al.*, 1992).

Precursors, Subsites, and Histology

The study by Tuyns *et al.*, (1988) showed a much stronger alcohol relation with cancer of the epilarynx as compared

TABLE 19.3 Relative Risk of Cancer of the Larynx According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Graham *et al.*	369	0	1		16.2	7.2
(1981)		0.1– 0.9	1.5	0.8–2.6		
U.S.		0.9– 12.9	1.3	1.8–2.1		
		13.0+	1.8	1.1–2.8		
Olsen *et al.*	326	0 - 14.3	1		25.7	3.9
(1985)		14.4– 28.6	1.5	1.1–2.1		
Denmark		28.7– 42.9	3.2	2.0–5.2		
		43+	4.1	2.4–7.1		
Tuyns *et al.*	814	0 - 20	1		8.2	0.8
(1988)		21 - 40	0.9	0.6–1.9		
Europe		41 - 80	1.1	0.8–1.5		
		81 -120	1.9	1.4–2.6		
		121+	2.9	2.2–3.9		
Franceschi *et al.*	388	0	1		2.7	1.4
(1994)		1.9– 24.2	0.6	0.3–1.1		
Italy		26.0– 50.2	0.4	0.3–0.6		
		52.1– 76.3	0.4	0.3–0.7		
		78.1–102.3	0.9	0.5–1.4		
		104.2+	1.1	0.7–1.7		
Dosemeci *et al.*	832	0	1		6.6	3.6
(1997)		0.5– 16	1.7	1.0–3.2		
Turkey		16.5– 64	1.8	1.1–2.9		
		64.5+	1.5	0.8–2.9		
Overall summary slope					10.5	2.9
	$D = 36$, d.f. = 4					

[a]All results are adjusted for at least age and smoking.

with cancer of the endolarynx. This finding has been long-cited as evidence that a direct effect of alcohol on tissues is the mechanism of alcohol's effect on head and neck cancers (Rothman, 1995). Other authors have not distinguished the epilarynx from lower structures, and from that perspective the Tuyns *et al.*, (1988) finding has not been replicated. Generally the anatomic subsites distinguished are the supraglottis and lower structures (e.g., glottis), and differences in association between these have not been consistently shown (Dosemeci *et al.*, 1997; Hedberg *et al.*, 1994).

Nuances

As with cancer of the oropharynx, some evidence suggests that alcohol consumed in beer or distilled spirits is more related to risk than an equal amount of alcohol consumed in wine (Olsen *et al.*, 1985; Williams and Horm, 1977). As noted above, however, imbalanced distribution of consumption of specific alcoholic beverages in a given population frequently hampers comparisons of beverage effects (Freudenheim *et al.*, 1992). The slightly greater slope in a study done among wine-drinking countries (Tuyns *et al.*, 1988) than in a study conducted in Turkey (Dosemeci *et al.*, 1997), where distilled spirits were preferred, somewhat weighs against differences in beverage-specific effects.

Esophagus

Slope and Heterogeneity

There is a clear dose–response relation between alcoholic beverage consumption and cancer of the esophagus (Table 19.4). The overall summary slope is less than for oropharyngeal cancer. As with the sites reviewed above, the strength of the association varies considerably. The slopes derived from studies conducted in France (Tuyns *et al.*, 1979) and Uruguay (De Stefani *et al.*, 1990) differ by nearly threefold. Unlike the cancer sites reviewed above, the studies with the weakest associations for esophageal cancer were not conducted in Italy, but in Uruguay (De Stefani *et al.*, 1990) and China (Gao *et al.*, 1994).

TABLE 19.4 Relative Risk of Cancer of the Esophagus According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Tuyns *et al.*	314	0 - 20	1		22.3	1.6
(1979)		21 - 40	1.1	0.6– 2.1		
(France)		41 - 60	2.5	1.4– 4.6		
		61 - 80	3.6	2.0– 6.4		
		81 -100	9.8	5.4–17.8		
		101 -120	10.9	5.8–20.7		
		121 -140	11.3	5.5–23.0		
		141+	23.3	14.7–42.7		
De Stefani *et al.*	199	0	1		6.6	1.0
(1990)		0.8– 19.2	0.9	0.4– 1.8		
Uruguay		20.0– 39.2	0.7	0.3– 1.6		
		40.0–119.2	1.4	0.8– 2.4		
		120 -199.2	3.6	1.9– 6.7		
		200.0+	5.3	2.7–10.2		
Cheng *et al.*	400	0	1		16.1	1.5
(1992)		0.1– 7	1.1	0.7– 1.8		
Hong Kong		7.1– 14.1	1.4	0.7– 2.7		
		14.3– 28.4	1.8	1.0– 3.4		
		28.6– 57.0	3.4	1.9– 6.0		
		57.1– 85.6	5.1	2.7– 9.4		
		85.7–114.1	11.1	5.4–22.9		
		114.3–142.7	18.1	7.4–44.1		
		142.9+	9.9	5.3–18.7		
Gao *et al.*	624	0	1		8.6	1.5
(1994)		0.1– 35.6	1.2	0.8– 1.8		
China		35.7–107.0	0.9	0.6– 1.3		
		107.1+	4.0	2.6– 6.3		
Franceschi *et al.*	410	0	1		9.5	1.3
(1994)		1.9– 24.2	1.0	0.5– 2.0		
Italy		26.0– 50.2	1.1	0.6– 2.0		
		52.1– 76.3	1.9	0.9– 3.9		
		78.1–102.3	2.8	1.2– 6.6		
		104.2+	3.7	2.2– 6.2		
Overall summary slope					12.6	2.8
	$D = 82$, d.f. $= 4$					

[a]All results are adjusted for at least age and smoking.
[b]Gannon *et al.* (1997) had 514 cases of esophageal carcinoma in their study; their results were not included in this table because they made the number of cases of adenocarcinoma and squamous carcinoma roughly equal by design, whereas in the studies included the mix was as it usually occurs, with about 20% of cases having adenocarcinoma.

Confounding and Interaction

The increased risk of esophageal cancer among heavy drinkers does not appear to be due to their diet (Franceschi *et al.*, 1994; Cheng *et al.*, 1992; Gao *et al.*, 1994) or to smoking. The effect of alcohol on risk of esophageal cancer among never smokers (Baron *et al.*, 1993; Tavani *et al.*, 1994) or among nonsmokers (Tuyns, 1983; Pottern *et al.*, 1981) has been reported consistently, with the exception of a study conducted in China (Gao *et al.*, 1994). Whether alcohol and smoking interact is unclear; studies show their joint effects as being either additive (Tavani *et al.*, 1993; De Stefani *et al.*, 1990; Graham *et al.*, 1990) or more than additive (Baron *et al.*, 1993; Gao *et al.*, 1994).

Precursors, Subsites, and Histology

Most epidemiologic studies of alcohol and esophageal cancer do not specify the histology of the tumors included and presumably reflect a mixture, with primarily squamous histology. Several studies, however, have focused on adenocarcinoma of the esophagus (Kabat *et al.*, 1993; Gao *et al.*, 1994; Brown *et al.*, 1994; Gammon *et al.*, 1997). While a modest dose–response relation is present in most adenocarcinoma studies (Kabat *et al.*, 1993; Gao *et al.*, 1994; Brown *et al.*, 1994), Gammon *et al.* (1997) found no relation with alcohol. Studies that contrast the alcohol relation between adenocarcinoma and squamous carcinoma clearly show a stronger relation with squamous tumors (Gao *et al.*, 1994; Gammon *et al.*, 1997, Kabat *et al.*, 1993).

Gao *et al.* (1994) presented results according to the location of the tumor in the esophagus and found that the relation with alcohol intake was slightly greater for the upper third of the esophagus. This observation suggests that the effect of alcohol on esophageal cancer is not merely due to alcohol-induced reflux of gastric contents.

Nuances

Early studies by Tuyns (1970) and Tuyns and colleagues (1979) in the Calvados region of France suggested that cider and its distillates (calvados) might increase risk of esophageal cancer more so than an equal amount of alcohol consumed in other beverages. A subsequent investigation of this issue in Calvados (Launoy *et al.*, 1997) also suggested differences among beverages, but cider and cold calvados were not implicated. Other data support that conditional on amount of ethanol consumed, intake of distilled spirits and beer (Gammon *et al.*, 1997) or moonshine (Brown *et al.*, 1988) is especially associated with risk.

Recent Japanese data suggest that having the heterozygous inactive ALDH genotype increases risk of esophageal cancer (Yokoyama *et al.*, 1996). Other Japanese data suggest that CYP2E1 genotype is not related to risk (Morita *et al.*, 1997).

Liver

Slope and Heterogeneity

Overall the data in Table 19.5 suggest a modest association between alcohol consumption and risk of hepatocellular carcinoma, although some studies show no relation (Trichopoulos *et al.*, 1987).

Confounding and Interaction

Confounding of the alcohol–liver cancer relation by smoking is not a major consideration because smoking is not a strong

TABLE 19.5 Relative Risk of Cancer of the Liver According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Stemhagen *et al.*	265	0	1		7.4	3.3
(1983)		0.1– 8.8	1.2	0.7–2.2		
U.S.		8.8–35.1	1.5	0.8–2.9		
		35.1–72.3	2.6	1.0–6.5		
		72.4+	2.4	1.0–5.7		
Trichopoulos *et al.*	194	0 – 9	1		0.5	2.3
(1987)		10 –39	0.7	0.5–1.2		
Greece		40 –69	0.9	0.6–1.5		
		70+	1.0	0.6–1.5		
Yu *et al.*	165	0 – 8.6	1		7.6	6.1
(1988)		9.6–27.8	1.2	0.8–1.9		
U.S.		28.8+	1.4	0.8–2.4		
Tsukuma *et al.*	192	0 –19.7	1		6.9	2.6
(1990)		19.7–78.9	1.0	0.6–1.6		
Japan		78.9+	2.2	1.2–4.0		
Tanaka *et al.*	204	0	1		9.9	3.9
(1992)		0.1–20.8	1.0	0.6–1.7		
(Japan)		20.8–47.0	1.1	0.6–1.8		
		47.0+	1.9	1.1–3.1		
Overall summary slope					5.7	1.9
	$D = 6$, d.f. $= 4$					

[a]All results are adjusted for at least age and smoking.

risk factor for liver cancer, if at all. Diet is also not a strong risk factor for liver cancer (Willett and Trichopoulos, 1996). The joint association of hepatitis and alcohol use with risk of liver cancer was examined in a Taiwanese study, and interaction under a multiplicative model was not apparent (Chen *et al.*, 1991).

Precursors, Subsites, and Histology

Heavy alcohol consumption is a risk factor for cirrhosis (Tuyns and Pequignot, 1984), and cirrhosis is a risk factor for hepatocellular carcinoma (La Vecchia *et al.*, 1988; Adami *et al.*, 1992). If all alcohol-induced liver cancer arises from cirrhosis, then one might expect risk of hepatocellular cancer among cirrhotics to be independent of history of alcohol use. In a study of cirrhotics in Sweden, the risk of hepatocellular carcinoma was the same regardless of alcohol history (Adami *et al.*, 1992), but in Japan alcohol consumption history in cirrhotics at the time of diagnosis of cirrhosis predicted subsequent risk of hepatocellular carcinoma (Ikeda *et al.*, 1993). Nonetheless, if alcohol can worsen cirrhosis, then the Japanese data may be compatible with the cirrhosis mechanism.

Nuances

For a given level of alcohol consumption, women are more likely to get cirrhosis than are men (Tuyns and Pequignot, 1984). This greater susceptibility is likely due to women having less gastric ADH, smaller bodies, and less lean body mass, as noted above. The stronger alcohol– liver cancer association in females observed by Stemhagen *et al.* 1983) and Yu *et al.* (1988) therefore fits with the hypothesis that alcohol is carcinogenic to the liver through a mechanism mediated by cirrhosis. To date, evidence that P450 2E1 genotype is related to risk of hepatocellular carcinoma among drinkers is not convincing (Lee *et al.*, 1997).

Pancreatic Cancer

Slope and Heterogeneity

The results of the studies in Table 19.6 show little or no support for an association, and statistically the slopes are homogeneous. The overall summary slope is near zero.

Nuances

Despite the lack of association between alcohol and risk of pancreatic cancer in epidemiologic data overall, a causal relation may exist. Heavy alcohol consumption causes chronic pancreatitis (Sarles *et al.*, 1989; Yen *et al.*, 1982), which has been shown to increase risk of pancreatic cancer (Lowenfels *et al.*, 1993) through a mechanism resembling that for alcohol causing liver cancer via cirrhosis. If mortality data (Schmidt and De Lint, 1972; Nicholls *et al.*, 1974; Robinette *et al.*, 1979) provide any indication of the frequency of conditions that occur in cohorts of alcohol drinkers, cirrhosis appears to be a much more common outcome of heavy alcohol consumption than is pancreatitis, and this may explain why alcohol intake is more strongly associated with liver cancer than with pancreatic cancer. In addition, cirrhosis increases risk of hepatocellular carcinoma much more than pancreatitis increases risk of pancreatic cancer (Ikeda *et al.*, 1993; Lowenfels *et al.*, 1993). Thus, the difficulty in observing an association between alcohol intake and pancreatic cancer in epidemiologic studies may stem in part from the rarity of the precursor condition among drinkers and its associated modest risk of pancreatic cancer.

Large Bowel Cancer

Slope and Heterogeneity

The overall summary slope in Table 19.7 is modest and its difference from zero is not statistically significant. Heterogeneity among study results was evident. The slope is nearly identical to results reported in an earlier metaanalysis (Longnecker *et al.*, 1990), which included 27 studies and in which heterogeneity was not found. In the earlier metaanalysis, results from follow-up studies showed a slightly stronger relation than did the case-control results (Longnecker *et al.*, 1990). More recent follow-up data are consistent with a weak dose–response relation (Goldbohm *et al.*, 1994), although some reports show a stronger relation (Giovannucci *et al.*, 1995).

Confounding and Interaction

When an association is found between alcohol consumption and risk of colorectal cancer, it does not appear to be due to confounding by other dietary factors (Potter and McMichael, 1986; Kune *et al.*, 1987; Longnecker, 1990; Peters *et al.*, 1992; Giovannucci *et al.*, 1995). The association of alcohol with risk of colorectal cancer has not been evaluated after adjusting for past smoking, a potential risk factor for colorectal cancer (Giovannucci and Martinez, 1996). However, because the magnitude of the purported past smoking–colorectal cancer risk association is moderate at best, it is unlikely that confounding by past smoking can account for all of the alcohol–colorectal cancer association. The strength of the alcohol–colorectal cancer association may depend on folate intake (Freudenheim *et al.*, 1991; Giovannucci *et al.*, 1995), but whether folate and alcohol act independently is not yet clear (Boutron-Ruault *et al.*, 1996).

Subsites, Precursors, and Histology

Alcohol consumption appears to be related to occurrence of adenomatous colorectal polyps, but on average the association is weak (Martinez *et al.*, 1995; Longnecker *et al.*, 1996). Debate continues about whether the association of al-

TABLE 19.6 Relative Risk of Cancer of the Pancreas According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Falk[b] *et al.*	203	0	1		6.0	3.5
(1988)		0.1– 11.0	2.0	1.1–3.0		
U.S.		11.1– 20.4	1.4	0.7–2.0		
		22.3– 48.3	1.1	0.7–1.9		
		50.1+	1.5	0.7–1.9		
Bouchardy *et al.*	494	0	1		−1.8	2.0
(1990)		0.1– 25.9	0.9	0.6–1.2		
Europe		26.0– 38.9	0.9	0.6–1.2		
		39.0– 51.9	1.1	0.7–1.7		
		52.0– 65.0	0.7	0.5–1.1		
		78.0– 91.0	1.0	0.6–1.6		
		104.0+	0.8	0.5–1.3		
Ji[b] *et al.*	245	0	1		−0.9	3.3
(1995)		0.1– 22.9	0.7	0.4–1.3		
China		23.0– 47.4	1.1	0.7–1.8		
		47.5– 80.6	0.9	0.5–1.4		
		80.7+	0.9	0.5–1.4		
Silverman[b] *et al.*	243	0	1		2.4	3.3
(1995)		1.9– 14.8	0.8	0.5–1.2		
U.S.		14.9– 40.8	0.9	0.6–1.5		
		40.9–105.8	0.9	0.5–1.5		
		105.9+	1.7	0.9–3.2		
Tavani *et al.*	361	0	1		1.5	2.2
(1997)		0.1– 52.0	0.9	0.7–1.3		
Italy		52.1– 91.0	1.1	0.7–1.7		
		91.1–104.0	1.4	0.7–2.7		
		104.1+	1.1	0.5–2.2		
Overall summary slope					0.8	1.2
	$D = 7.3$, d.f. $= 4$					

[a]All results are adjusted for at least age and smoking.
[b]Results presented for males only.

coholic beverage consumption is greater if the alcohol is consumed in beer, and about whether the association is greater for rectal cancer than for colon cancer (Newcomb *et al.*, 1993). The results of the earlier metaanalysis gave some support for the association being stronger for beer, but not for a difference in association between colon and rectal cancer (Longnecker *et al.*, 1990).

Breast Cancer

Slope and Heterogeneity

Table 19.8 shows that a modest dose–response relation is present in most of the largest studies of breast cancer, and that the slopes of the studies are statistically homogeneous. Notably, the alcohol–breast cancer association appears to be stronger than that for liver cancer, for which a causal link with alcohol is generally accepted. The overall summary slope and standard error shown in Table 19.8 agree closely with those calculated in a metaanalysis of 38 studies that used the same quantitative approach (Longnecker, 1994). The similarity seen here—and for colorectal cancer—provides empiric validation of the approach of using the five largest studies to estimate the dose–response relation for a given cancer site. In the earlier metaanalysis (Longnecker, 1994), however, statistical heterogeneity among breast cancer study results was present, and assessment of heterogeneity on the basis of a larger number of studies probably gives a more robust result.

Several factors may contribute to the heterogeneity observed in the 1994 metaanalysis. The size of the association was greater in countries with higher per capita alcohol consumption. For example, studies from Sweden tended to find little or no association, and studies from Spain, France, and Italy tended to find the strongest [e.g., the La Vecchia *et al.* (1989) study in Table 19.8]. This is in contrast with the asso-

TABLE 19.7 Relative Risk of Cancer of the Large Bowel According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Williams and Horm	1061	0	1		5.5	3.3
(1977)		0.1–30.6	1.1	0.9–1.4		
U.S.		30.7+	1.3	1.1–1.6		
Kune[b] *et al.*	388	0	1		0.9	4.0
(1987)		0.1–16.0	1.4	0.8–2.5		
Australia		16.1–40.0	1.1	0.6–1.9		
		40.1+	1.2	0.7–2.0		
Barra *et al.*	1470	0	1		−2.4	1.9
(1992)		1.9–24.2	0.9	0.7–1.3		
Italy		26.0–50.2	1.0	0.8–1.4		
		52.1–76.3	1.0	0.8–1.5		
		78.1+	0.7	0.5–1.0		
Peters *et al.*	746	0	1		9.4	3.5
(1992)		0.4– 4.3	0.8	0.6–1.2		
U.S.		4.7–12.5	1.0	0.7–1.5		
		12.9–31.8	0.9	0.6–1.3		
		32.3–42.6	1.3	0.8–2.0		
		43.0+	1.7	1.1–2.5		
Newcomb *et al.*	779	0	1		12.3	4.6
(1993)		1.9– 3.7	1.0	0.8–1.2		
U.S.		5.6– 9.3	1.1	0.8–1.4		
		11.1–18.6	1.1	0.7–1.5		
		20.5+	1.5	1.0–2.2		
Overall summary slope					4.4	2.9
	$D = 22$, d.f. $= 4$					

[a]All results are adjusted for at least age and smoking.
[b]Results presented for males only.

ciation for most sites, for which the results from studies in Italy tend to show weaker associations. The length of follow-up in cohort studies was another attribute that was related to the heterogeneity in results across studies (Longnecker, 1994). For example, one of the studies finding an inverse relation between alcohol intake and breast cancer risk was the Framingham study, a very old study in which the alcohol intake data were collected early in the women's lives. Due to changes in consumption after intake was ascertained, the association may have been obscured.But length of follow-up and per capita intake together account for only a small portion of the variation in association across studies, and much of the variation remains unexplained.

Confounding and Interaction

Numerous studies have evaluated whether known or established breast cancer risk factors can account for the alcohol–breast cancer association, but no important confounders have been identified (Longnecker, 1994). Similarly, investigations of potential effect modifiers have not given consistent results. A report from the Nurses Health Study in 1990 suggested that the alcohol–breast cancer association was greater among women using hormone replacement therapy (Colditz *et al.*, 1990). Gapstur *et al.* (1992) also reported a similar finding. However, subsequent analyses from the Nurses' Health Study which included a larger number of cases did not confirm earlier findings (G.A. Colditz, personal communication, 1997). Several other studies have looked at this issue and found no evidence of interaction (Friedenreich, 1994; Longnecker *et al.*, 1995a,b; van den Brandt *et al.*, 1995). On balance, the evidence suggests that use of hormone replacement therapy does not affect the association of alcohol with breast cancer. Alcohol appears not to be a risk factor for breast cancer in men (Casagrande *et al.*, 1988).

Precursors, Subsites, and Histology

Alcohol use appears not to be related to mammographic density, which is a strong risk factor for breast cancer (Byrne

TABLE 19.8 Relative Risk of Cancer of the Breast According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Garfinkel *et al.*	2933	0	1		5.5	2.0
(1988)		6.5	1.0	0.8–1.1		
U.S.		13.0	1.2	1.0–1.3		
		26.0	1.1	0.9–1.3		
		39.0	1.2	0.9–1.7		
		52.0	1.3	0.8–1.9		
		65.0	1.9	1.1–3.3		
		78.0+	1.7	1.1–2.6		
Chu *et al.*	3498	0	1		3.0	3.4
(1989)		0.1– 1.8	1.0	0.8–1.1		
U.S.		1.9– 5.6	1.0	0.8–1.2		
		7.4–13.0	0.9	0.7–1.1		
		14.9–26.0	1.1	0.9–1.3		
		27.9–39.0	1.0	0.8–1.4		
		40.9+	1.2	0.9–1.6		
LaVecchia *et al.*	2402	0	1		12.1	2.2
(1989)		0.1–12.9	1.3	1.1–1.6		
Italy		13.0–25.9	1.3	1.1–1.5		
		26.0–39.0	1.4	1.2–1.7		
		39.1+	2.2	1.7–2.7		
Longnecker *et al.*	6662	0	1		8.8	2.1
(1995a)		0.1– 5	1.1	1.0–1.2		
U.S.		6 –11	1.1	1.0–1.2		
		12 –18	1.2	1.0–1.4		
		19 –32	1.5	1.2–1.8		
		33 –45	2.0	1.4–2.7		
		46+	2.0	1.4–2.7		
Smith-Warner[b] *et al.*	4335	0	1		6.8	1.9
(1997)		30+	1.4	1.2–1.6		
Developed						
Overall summary slope					7.6	1.4
	$D = 7.6$, d.f. = 4					

[a]All results are adjusted for at least age and smoking.

[b]Results were taken from an abstract that presented a summary slope and results for only the highest drinking category.

et al., 1995). Alcohol consumption is associated with increased risk of breast carcinoma *in situ* (Longnecker, *et al.*, 1995b). Several investigators have suggested that the alcohol–breast cancer relation depends on the estrogen receptor or progesterone receptor status of the tumor (Gapstur *et al.*, 1995; Nasca *et al.*, 1994), but results of these studies have been mixed. Histology-specific associations have not been reported.

Nuances

To address the issue of whether a woman who decreases her alcohol consumption could expect a reduction in breast cancer risk, we evaluated large studies with age-specific exposure data and found mixed results. While Harvey and colleagues (1987) found that drinking early rather than later in life was associated with increased risk, the four-state study (Longnecker *et al.*, 1995b) suggested no clear difference between past and recent consumption, and the most recent study we evaluated (Swanson *et al.*, 1997) suggested that recent consumption was most associated with risk. Clearly, distinguishing between the effects of past and recent consumption is difficult, most probably because past and recent intake are correlated. Perhaps the best summary of the matter, given present knowledge is that it is lifetime consumption that is the best predictor of risk. Three alcoholic drinks over a lifetime was associated with a relative risk of 2.3 in the four-state study (Longnecker *et al.*, 1995a). This is larger than the association in the metaanalysis, as expected, because the metaanalysis was essentially about recent intake.

If one accepts that drinking at any age contributes to risk, then decreasing consumption among adult women should decrease risk. Data from a case-control study in Los Angeles suggest that a woman who drank one drink daily until age forty and then quit drinking would decrease her risk by 11% compared to what she would have experienced had she kept drinking that amount (Longnecker *et al.*, 1995b).

Whether alcohol causes breast cancer is unclear. While the data are compatible with a dose–response relation, the weakness and inconsistency of the association leaves open the possibility that the association is due to the effect of some unidentified breast cancer risk factor that itself is associated with alcohol consumption. Some of the inconsistency in results across studies may arise because a weak association may appear to be absent in some studies. Statistical heterogeneity in effect size exists as well, although this is also true for many sites where alcohol is thought to be causal. Numerous biologically plausible mechanisms linking alcohol to breast cancer have been proposed; but evidence for any one is rather uncompelling. Animal models of mammary carcinogenesis provide inconsistent support for a relation. Singletary (1997) has developed an animal model that shows that alcohol increases mammary carcinogenesis and increases the density of the terminal end buds of the rat mammary gland, providing a mechanism for the increased risk. Of note is that the alcohol-treated animals do not have higher estrogen levels.

Two or more drinks per day is associated with an increased risk of death from all causes in women (Holman *et al.*, 1996); therefore, two drinks a day or more is too many. But for women who drink lightly or moderately, whether to continue drinking that amount is a more difficult question. Imagine, for example, a woman at low risk of heart disease, for whom low or moderate alcohol consumption give little benefit (Fuchs *et al.*, 1995). If we consider that about 25% of women are at low risk of cardiovascular disease (Fuchs *et al.*, 1995), and that about half of these women will have an above-average risk of breast cancer, then roughly 15% of women who drink lightly or moderately could have an increased total mortality because of alcohol-induced breast cancer. In such women, however, the increase in total mortality due to alcohol is likely to be small, in part because breast cancer accounts for only a fraction of all deaths.

In studies where the authors have presented results so that beverage-specific associations can be compared (Willett *et al.*, 1987; Harvey *et al.*, 1987; Rohan and McMichael, 1988; Howe *et al.*, 1991; Friedenreich *et al.*, 1993; Longnecker *et al.*, 1995a, van den Brandt *et al.*, 1995; Swanson *et al.*, 1997), a tendency is seen for wine not to be most strongly associated with risk–only one (Friedenreich *et al.*, 1993) of the nine studies found that the association was greatest for wine. In these studies, however, the differences between beverages are generally not statistically significant. New data from pooled cohort studies are the best available to address this issue, and those data provide no compelling evidence of differences in association among beverages (Smith-Warner *et al.*, 1998).

Endometrial Cancer

More often than not alcohol consumption shows an inverse association with risk of endometrial cancer, although the results vary (Table 19.9). If alcohol increases estrogen levels (Longnecker, 1993), one would expect alcohol to be clearly associated with an increased risk of cancer of the endometrium. The lack of a clear relation between alcohol and endometrial cancer, however, suggests that alcohol has no substantial effect on estrogen levels, and further suggests that the alcohol–breast cancer relation is mediated by a mechanism other than estrogens.

Lung Cancer

Alcohol use was associated with increased risk in four of the five largest studies of alcohol and lung cancer that met our inclusion criteria for review (Williams and Dorm, 1977; Bandera *et al.*, 1992; De Stefani *et al.*, 1993; Murata *et al.*, 1996; Dosemeci *et al.*, 1997). We chose not to summarize these data in a table, however, because the associations in these studies are likely to be due to residual confounding caused by failure to adjust for recency of smoking, or by misclassification of smoking. Authors frequently adjusted alcohol estimates for pack-years of cigarettes smoked, but failure to adjust for current smoking, which is likely to be associated with alcohol use, could cause alcohol to appear to be a risk factor when in fact it is not. Even with adjustment for pack-years of smoking as well as recency of smoking, misclassification of smoking may still make it appear that alcohol were causal when, in fact, it may not be (Morrison, 1984).

Other Malignancies

Multiple studies have found that alcohol consumption is not associated with risk of prostate cancer (World Cancer Research Fund, 1997; Longnecker and Enger, 1996), although two recent studies showing an association suggest this issue is still open (Hayes *et al.*, 1996; De Stefani *et al.*, 1995).

The association of alcoholic beverage consumption with other malignancies has been recently reviewed elsewhere (World Cancer Research Fund, 1997; Longnecker and Enger, 1996), and no other notable associations were identified. Wu *et al.*, (1997) recently found that alcohol consumption was associated with an increased risk of cancer of the small intestine. Recent reports that maternal alcohol intake increases the risk of leukemia in offspring (Shu *et al.*, 1996) merits further investigation.

TABLE 19.9 Relative Risk of Cancer of the Endometrium According to Level of Alcohol Consumption[a]

Author Year Place	Cases	Ethanol (grams/day)	RR	(95% CI)	β × 1000	SE (β) × 1000
Williams and Horm	345	0	1		−11.0	4.6
(1977)		0.1–30.6	0.7	0.4–0.9		
U.S.		30.7+	0.6	0.4–1.1		
Webster *et al.*	337	0	1		−17.8	6.8
(1989)		0.1– 7.0	0.9	0.6–1.2		
U.S.		7.1–21.3	0.6	0.4–0.9		
		21.4+	0.5	0.3–0.9		
Swanson *et al.*	400	0	1		−11.9	13.9
(1993)		0.1– 0.8	0.8	0.5–1.2		
U.S.		1.9– 7.4	1.0	0.6–1.8		
		7.5+	0.7	0.4–1.4		
Parazzini*et al.*	726	0	1		11.5	4.1
(1995)		0.1–13.0	1.1	0.9–1.4		
Italy		13.1–26.0	1.4	1.1–1.8		
		26.1+	1.6	1.2–2.2		
Newcomb *et al.*	739	0	1		0.3	4.5
(1997)		0.1– 1.8	1.2	1.0–1.6		
U.S.		1.9– 3.7	0.9	0.7–1.1		
		5.6–11.1	1.1	0.8–1.5		
		13.0–24.1	0.8	0.6–1.1		
		26+	1.3	0.8–2.1		
Overall summary slope					−4.8	6.0
	$D = 20$, d.f. = 4					

[a]All results are adjusted for at least age and smoking.

COMPARISON OF THE EFFECT SIZE ACROSS SITES

The risk of cancer associated with alcoholic beverage use is greatest for the organs that first come in direct contact with ingested alcohol, such as head and neck cancers, suggesting that alcohol use exerts a direct carcinogenic effect on these tissues (Rothman, 1995). The effects of alcohol on risk of cancer of the larynx and on the esophagus are nearly the same, however, raising the possibility that part of alcohol's effect on these organs may be via the bloodstream. The lack of association of alcohol use with cancer of the stomach also suggests that not all of alcohol's effects are due to direct action on mucosal surfaces, although the stomach may be protected by dilution of ingested material and by it ADH.

The results in Figure 19.2 show that the association of alcohol with cancers of the large bowel and breast are about as large or larger than its association with liver cancer. While there is general agreement that alcohol causes liver cancer, this is not the case for cancers of the large bowel and breast. The difference in attributing causality for these sites is due to lack of knowledge about mechanism. For liver cancer, the alcohol-cirrhosis-cancer sequence is widely accepted, whereas for cancers of the large bowel and breast, the mechanisms are not clear.

POTENTIAL MECHANISMS OF ALCOHOL CARCINOGENESIS

A dogma in alcohol carcinogenesis has been that in animal models alcohol is not a carcinogen [International Agency for Research on Cancer (IARC), 1988; Anderson *et al.*, 1995]. But in recent studies numerous examples exist of alcohol-promoted carcinogenesis (Mufti *et al.*, 1993). In fact, multiple mechanisms exist by which alcoholic beverage consumption may cause cancer.

a. Carcinogenicity of acetaldehyde. Acetaldehyde is a carcinogen in animal modes (IARC, 1988). That alcohol itself does not appear to be a carcinogen, although it is metabolized to acetaldehyde, is a curious finding. Techniques for measuring acetaldehyde adducts have recently improved and show that adducts are detectable in the blood of drinkers (Fang and Vaca, 1997). In a recent report, drinkers who were heterozygous for inactive ALDH were at increased risk of cancers of the upper aerodigestive tract (Yokoyama *et al.*, 1996). Confirmation of this finding would help establish an acetaldehyde mechanism of carcinogenesis, but not all of the carcinogenic effect of alcohol may be by this mechanism.

b. Oxidative stress due to alcohol metabolism. Metabolism of alcohol is associated with increased production of free radicals (Mufti *et al.*, 1993), which have been implicated in carcinogenesis.

c. Competitive inhibition of the metabolism of other carcinogens. The metabolism of carcinogens in animal experiments has been slowed by concurrent administration of alcohol, possibly due to competitive inhibition of metabolism by P4502E1. In these models, alcohol caused increased formation of carcinogen–DNA adducts and tumor incidence (Anderson *et al.*, 1995).

d. Impairment of nutrient metabolism. Heavy alcohol consumption interferes with absorption and metabolism of folate (Freudenheim *et al.*, 1991), and folate deficiency increases risk of cancer of the liver and large bowel in animals (Giovannucci *et al.*, 1995). In addition, heavy alcohol intake alters metabolism of β-carotene and vitamin A, and these alterations may increase risk of cancer (Albanes *et al.*, 1996; Ahmed *et al.*, 1994).

e. Alterations of hormone levels. Relations between alcohol intake and altered hormone levels, especially estrogens, have been found, but the results are inconsistent (Reichman *et al.*, 1993; Dorgan *et al.*, 1994; Hankinson *et al.*, 1995). Hormone alterations among the heaviest of drinkers or among cirrhotics may be entirely different than in those drinking several drinks per day or less.

f. Carcinogenicity of congeners. Products of fermentation, preservatives, and flavoring agents are examples of congeners in alcoholic beverages. Acetaldehyde is a congener in all alcoholic beverages, but the concentration of ethanol is about one million fold greater (IARC, 1988). That ratio, or an even larger one, is typical for congeners. Because the ratio is so high, and because alcohol has pharmacologic effects at the doses used, it seems likely that much, if not all, of the association of alcoholic beverage consumption with cancer risk is due to ethanol.

On the other hand, differences between beverages in congener content may explain findings of interbeverage differences in association. Rothman *et al.*, (1989), for example, found a greater association of hypopharyngeal cancer with dark as compared with light distilled spirits. Other studies have also suggested stronger associations of cancer with beer or distilled spirits than with wine (Blot *et al.*, 1988; Olsen *et al.*, 1985; Williams and Horm, 1977; Brown *et al.*, 1988; Gammon *et al.*, 1997). Wine contains resveratrol, which may be an anticarcinogen (Jang *et al.*, 1997), although whether this substance is absorbed in physiologically significant amounts is not established (Soleas *et al.*, 1997). Nevertheless, disentangling congener effects from the effects of different patterns of alcohol use (e.g., with or without food) makes it difficult to establish that interbeverage differences in association are due to congeners.

g. Other mechanisms. In animal models, administration of alcohol increases cell proliferation in the mouth, esophagus, rectum (Simanowski *et al.*, 1995), and in mammary terminal end buds (Singletary *et al.*, 1991). Increased cellular turnover increases risk of neoplasia (Preston-Martin *et al.*, 1993). Alcohol also has a wide range of adverse effects on the immune system in humans and in animal models (Watson *et al.*, 1994) that may increase susceptibility to cancer. Other potential mechanisms, such as altered membrane fluidity, alterations in carcinogen metabolism due to induction of CYP2E1 or other effects of alcohol on P450 expression, alcohol-enhanced penetration of carcinogens across mucosal membranes, and displacement of dietary nutrients are discussed in detail elsewhere (Garro and Leiber, 1990; Longnecker, 1995; Freund, 1979).

GENDER DIFFERENCES

Gender differences in alcohol effects may help provide insight into the carcinogenic mechanism. Differences in metabolism (as discussed in the section Ethanol Metabolism, p. 277) would suggest stronger associations with alcohol in women than in men for cancer sites in which the mechanism involves exposure through the bloodstream rather than direct contact. Indeed, for laryngeal cancer, two of the five studies in Table 19.3 (Franceschi *et al.*, 1994; Choi and Kahyo, 1991) presented gender-specific results and both showed a stronger association in females, but the small number of women limits its conclusions. Three of five studies we reviewed for liver cancer also presented sex-specific results (Yu *et al.*, 1988; Stemhagen *et al.*, 1983; Tanaka *et al.*, 1992) and also found a stronger association in women. However, for colorectal cancer, no gender difference was found in an earlier meta-analysis (Longnecker *et al.*, 1990).

For organs that come in direct contact with ingested alcohol, the data overall give no clear indication of a gender difference in association with cancer risk (Blot *et al.*, 1988; Franceschi *et al.*, 1994; Tuyns, 1983; Kabat and Wynder, 1989).

In general, comparison of alcohol effects between women and men is hampered by the small number of female drinkers, especially heavy drinkers, relative to males. Thus, overall, it remains unclear if the effect of alcohol differs by gender for any cancer site except the breast, although data for laryngeal and liver cancer are suggestive of a greater effect in females. If, in fact, the risk for oral cavity and esophageal cancers is the same for males and females, and risk of laryngeal and liver cancer is greater for females, it suggests that the alcohol effect for oral cavity and esophageal cancers is at least in part via a topical mechanism.

POPULATION ATTRIBUTABLE RISKS

Using the summary betas estimated for each site, we calculated population attributable risks (PAR) for alcohol consumption using the methods described in the Appendix. Estimated PARs for cancers likely to be associated with alcohol consumption are shown in Table 19.10. Based on cancer statistics from SEER (Ries *et al.,* 1994), almost 23,400 (1.9%) of new cases of all cancer in 1994 are attributable to alcohol consumption. If sites for whom the alcohol–cancer association has not yet been established (pancreas, large bowel, and breast) are excluded from the calculations, the number of cancer cases attributable to alcohol consumption drops to 7,187 (0.6%).

Previous estimates of the proportion of cancer due to alcohol consumption have been higher than ours. Franceschi *et al.,* (1990) estimated that 55% of oral cancers, 45% of pharyngeal cancers, 26% of laryngeal cancers, and 52% of esophageal cancers in Italy were attributable to alcohol use. The PARs in Italy may be high because of the greater alcohol consumption in that country. Other estimates of PAR may be higher because they assumed stronger associations between alcohol and cancer. Tanaka *et al.,* (1988), for example, observed a stronger association between alcohol consumption and liver cancer than our summary beta, and the corresponding proportion of hepatocellular carcinoma due to alcohol consumption in Japan was estimated to be 22%. Rothman and Keller (1972), estimated that 43% of oral cancer was attributable to alcohol consumption, but again these were based on data showing a stronger association between alcohol and cancer than we found in this review. The tendency for published PARs for alcohol to be greater than ours may reflect a tendency of authors to present PARs only when they are high.

Stronger assumed associations between alcohol and cancer probably also contributed to higher estimates of the proportion of all cancer deaths attributable to alcohol made by Doll and Peto (1981) and by Rothman *et al.* (1980). Doll and Peto (1981) estimated that roughly two-thirds of deaths in men from cancer of the mouth, pharynx, larynx, and esophagus and one-third of these deaths in women are attributable to alcohol. They concluded that about 3% of all cancer deaths are attributable to alcohol consumption. Rothman *et al.* (1980) estimated that 30–75% of deaths from cancer of the mouth, pharynx, larynx, esophagus, and liver are alcohol-related and arrived at the same estimate of 3%. In the present analyses, we found a much smaller proportion of cases at each alcohol-related cancer site to be attributable to alcohol consumption. In summary, we estimate that less than 2% of all cancers are attributable to alcohol consumption, a smaller figure than has been previously suggested.

TABLE 19.10 Proportion of Cancer Cases Attributable to Alcohol Consumption, By Site

Cancer	Number of cancer cases	Population Attributable Risk (%)	Number attributable to alcohol
Oral[a]	17,100	14.1	2,411
Pharyngeal	9,200	17.7	1,628
Laryngeal	12,500	8.4	1,050
Esophageal	11,000	10.3	1,133
Liver	16,100	4.4	708
Pancreas	27,000	0.6	162
Large bowel	149,000	3.4	5,066
Breast	183,000	6.0	10,980
Total	1,208,000	1.9[b]	23,139[b]
		0.6[c]	6,931[c]

[a]Excludes lip.

[b]Alcohol-related cancer sites included in these calculations were oral, pharyngeal, laryngeal, esophageal, liver, pancreas, large bowel, and breast.

[c]Alcohol-related cancer sites included in these calculations were the same as above but excluded pancreas, large bowel, and breast.

CONCLUSIONS

The International Agency for Research on Cancer (IARC, 1988) concluded that alcoholic beverages were a cause of cancer in humans for the following sites: mouth, pharynx, larynx, esophagus, and liver. It further concluded that the data for breast and large bowel cancer were suggestive but inconclusive. The present data still support the IARC conclusions.

However, the data in this review also suggest that the association of breast cancer with alcohol consumption is larger than the association with liver cancer, and that it is primarily lack of an established mechanism that precludes conclusions regarding causality. The same may hold for colorectal cancer, although the epidemiologic data are somewhat less convincing than for breast cancer. The lack of consistent association between alcohol and risk of endometrial cancer suggests that if alcohol causes breast cancer, estrogens are unlikely to mediate the effect.

Some support was found for the alcohol effect on the larynx being mediated via the bloodstream. There is evidence that the association is greater in females than males, and the magnitude of the association is similar to that of cancer of the esophagus, which comes in direct contact with the beverage. It is likely that alcohol also causes pancreatic cancer, but this outcome is so rare that epidemiologic data cannot detect the relation. Although data suggest an association between alcohol and lung cancer, the possibility that this is due to residual confounding by smoking precludes interpretation of the association as causal.

The mechanism by which alcoholic beverage consumption causes human cancer is not established, although support is increasing for at least some of the risk being due to alcohol's metabolism to acetaldehyde, an established carcinogen in animal models.

The data reviewed show that for many sites the dose–response relation is monotonic. If one chooses a category of light or moderate alcohol consumption in any given study, the confidence intervals for the relative risk will generally include one. But overall, the consistent presence of the dose–response relation for many sites suggests that risk is proportional to dose, even at light and moderate intakes.

The proportion of cancers attributable to alcohol consumption is less than 2%. The potential cancer risk associated with alcohol consumption should be balanced against other health effects of alcohol, including the benefits on cardiovascular disease. Advising those who drink lightly or moderately to abstain could be unwise because of the U-shaped relation between alcohol and total mortality. A reasonable public health message is that if you choose to drink, do not drink too much.

APPENDIX

We calculated population attributable risks (PAR) for alcohol consumption using the following equation given by Kleinbaum *et al.* (1982):

$$\mathrm{PAR} = 1 - \frac{1}{\sum_{i=0}^{k} p_i \mathrm{RR}_i} \tag{1}$$

for four ($k = 3$) levels of alcohol exposure, where p_i represents the proportion exposed, and RR_i represents the relative risk of cancer for the ith level of alcohol consumption. Categories of alcohol exposure were nondrinkers (0 g/d), light drinkers (less than half a drink per day, 0.1–6.4 g/d), moderate drinkers (half a drink to less than 2 drinks per day, 6.5–25.9 g/d), and heavy drinkers (at least 2 drinks per day, > 26 g/d). The approximate proportions of the U.S. population assumed in each drinking category were, respectively, 0.34, 0.33, 0.23, and 0.10 (Hurley and Horowitz, 199). RR_i was calculated for the estimated median intake for each category using the summary β for each site. We estimated the median level of ethanol intake for each category as 0 g, 1.7 g, 12.0 g, and 42.0 g ethanol per day based on the sex and age distribution of the U.S. population (U.S. Bureau of the Census, 1996) and information on drinking amounts for each sex-age group, as described elsewhere (Longnecker *et al.*, 1990).

We chose to use Eq. (1) as a simple way of approximating the PAR for each cancer site, although in the presence of confounding it may not estimate PARs accurately (Whittemore, 1983). An alternative formula for PAR,

$$\mathrm{PAR} = 1 - \sum_{i=0}^{k} \frac{p_{ci}}{\mathrm{RR}_i} \tag{2}$$

can be used with the adjusted RR to estimate an adjusted PAR (Bruzzi *et al.*, 1985), where p_{ci} represents the proportion of cases exposed. Other methods have also been developed to calculate adjusted PARs (Benichou, 1991; Gefeller, 1992). However, because we did not have the raw data from studies needed to take potential confounders into account in our PAR estimates, we assessed whether using adjusted RRs in Eq. (1) produced reasonable approximations of more properly adjusted PARs, obtained using adjusted RRs in Eq. (2). We used data on age, alcohol intake, smoking, and esophageal cancer provided in Breslow and Day (1980) from Tuyns *et al.* (1977) to compare PAR estimates for alcohol, with age and smoking as potential confounders. A comparison of "adjusted" PARs estimated both ways showed little difference between the two. This suggests that the PARs estimated in this review are reasonable approximations of adjusted PARs that could be calculated given the raw data.

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